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Terms: **titl (surfac coating) and stent** (Edit Search)

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*Pat. No. 5997517, **

5,997,517

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Bonding layers for medical device **surface coatings**

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pretreat w/ low pressure O-plasma

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CORE TERMS: coating, layer, polymer, adhesion, sample, wire, wet, acrylic, catheter, bond coat, copolymer, coat, substrate, micron, coated, hydrogel, dry, tie, medical device, tested, lubricity, plus, ethylene, reactive, acrylic acid, bonding, dried, bond, thin, hydroxyl

ABST:
A medical device is coated with a thin coherent bond coat of acrylics, epoxies, acetals, ethylene copolymers, vinyl polymers, polymers containing hydroxyl, amine, carboxyl, amide, or other reactive groups, and copolymers thereof. Outer layers may be applied and remain adherent to the substrate in water for an extended period. The bond coat may comprise cross linkers such as urea resins, melamines, isocyanates, and phenolics. Preferred polymers include vinylpyrrolidone-vinyl acetate, styrene acrylic polymer, ethylene acrylic acid copolymer, carboxyl function acrylic polymer, hydroxyl function acrylic polymer, and acrylic dispersion polymer. The coatings may be applied to inert metal or plastic surfaces of medical devices such as needles, guide wires, catheters, surgical instruments, equipment for endoscopy, wires, **stents,** angioplasty balloons, wound drains, arteriovenous shunts, gastroenteric tubes, urethral inserts, laparoscopic equipment, pellets, and implants. Methods of coating and coating liquids are provided.

NO-OF-CLAIMS: 23

EXMPL-CLAIM: 1

NO-OF-FIGURES: 0

NO-DRWNG-PP: 0

SUM:

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to an adhesive coating for a medical instrument. More specifically, the invention relates to polymer compositions which, when applied to an insertable medical device, provide for improved adhesion of a coating to the surface of the device, and related methods.

2. Related Art

Medical devices such as catheters or guide wires are inserted through trachea, blood vessels, urethra or other celoms or tissues, or through catheters or drainage tubes etc. Such devices are required to have a high degree of smoothness to assure introduction of such devices without causing trauma to tissue encountered during placement. These surfaces may be further enhanced by having lubricity for preventing injury or inflammation of mucous membrane which would be caused when the devices remain in the tissue. Other requirements for medical device surfaces have also been recognized.

In some instances, it is advantageous for medical device surfaces to have the capability of serving as a depot for various physiologically active substances such as anti-thrombogenic substances, anti-microbial substances, anti-neoplastic substances, genetic materials, hormones, living cellular materials and others. Anti-thrombogenic materials, such as complexes of heparin with quaternary ammonium compounds, are used on medical device surfaces to prevent formation of blood clots on the surface, which can form rapidly on vascular prostheses in vitro. Antimicrobial agents including penicillins, cephalosporins, fluoroquinolones, aminoglycocides, silver, compounds, phenol compounds, biguanides and others have been proposed for use in surface coatings to control nosocomial infections that often occur on surfaces of implanted prostheses, U.S. Pat. No. 5, 069,899, U.S. Pat. No. 5,525,348, and U.S. Pat. No. 4,442,133.

The construction of devices such as guide wires and catheters presents special problems for insertion. Guide wires generally include coiled guide wires formed of stainless steel and monofilament guide which may have plastic materials such as polyurethanes, polyamides, plolyolefins, etc. extruded over them to provide a surface to which coatings can adhere, and to provide smoothness and uniformity of the surface.

Catheters typically consist of plastic tubes which may have a single lumen or multiple lumens. Catheters may have balloons fastened along the tube to obstruct a vessel or to fix the catheters in a desired position. Catheters may also have ports at the distal end, side ports along part of the length, or other mechanical features needed to accomplish the particular device mission. Catheters may consist of a continuous length of tubing, or may comprise two or more sections of tubing consisting of similar or dissimilar materials which are welded together in order to have different properties at different locations along the length of the device. Catheters may be tapered, both within a segment or by having segments of differing diameters. Typical material of which catheters are constructed include polyamides, polyurethanes, vinyls such as polyvinylchloride, polyesters, polyolefins, silicones, and others. Typical diameters range from less than one millimeter to more than 8 millimeters.

As typically encountered in inserting a catheter, at the predetermined site, the guide wire tip is inserted through a catheter up to its tip opening, the catheter with the guide wire is inserted into for example a blood vessel percutaneously, and the catheter is further inserted through the vessel by using the guide wire as a leading and supporting guide. These operations produce friction and abrasive forces that apply to the surfaces of the medical device. It is desirable for the frictional resistance between the catheter inner surface and the guide wire to be low. Relatively high friction between the catheter and the guide wire not only prevents the guide wire from being inserted through the catheter, but the guide wire from being easily moved through the catheter, making it difficult to carry out subtle indwelling operations at the destined vessel site. Sometimes the guide wire cannot be withdrawn from the catheter, rendering the catheter lumen unusable despite the completion of the indwelling operation.

To avoid such problems, attempts have been made in the prior art to apply low frictional resistance Teflon and silicone oil to the outer surface of guide wires. Application of silicone oil fails to retain lubricity because of immediate loss of silicone coatings. Frequent applications add to frictional resistance, also undesirably creating troubles as mentioned above.

There is thus the need for a catheter and guide wire having a lower frictional resistance surface which enables more subtle operation in a vessel and can be easily inserted and remain at the site where catheters are otherwise difficult to manage during placement.

Polyurethane coatings have been applied directly on metal surfaces. U.S. Pat. NO. 4,876,126. However, commercial versions of this technology require thick layers (60-80 microns thick) in order to perform adequately. In practice, the thick layer extends continuously around the coated metal substrate. These layers have good cohesive forces and thus appear to be tightly bound on the metal surface, even though these layers do not necessarily have good adhesion to the metal surface. A disadvantage of such coatings is that because the polyurethane and other plastic layers are so thick, the metal diameter of the underlying wire must be correspondingly diminished. This is especially troublesome on the very fine wires such as those used in coronary angioplasty or neurointerventional catheterization procedures. These wires have OD's of about 0.010" (about 250 microns) and may have the majority of the diameter (about 120 to 170 microns) composed of plastic materials instead of metals. An alternate method is the use of low frictional materials such as polytetrafluoroethylene coatings which have lower friction than metals and most other plastic materials and which can be applied directly onto metallic substrates. Other materials such as high density polyethylene have been tried, but the coefficients of friction are not low enough for such materials. Oils have been applied, and the coefficients of friction are low. However, such treatments are transient because they wear off during use.

Hydrogel coatings are known to provide a lubricious surface for insertable devices. However, metals and certain plastic materials such as polyolefins, polyamides, silicones, polyesters and some others have inert surfaces and it is often difficult to achieve acceptable adhesion when applying surface coatings, including hydrogel coatings, over such surfaces.

Hydrogels can absorb several times their weight in water when placed in an aqueous environment. Usually, hydrogel layers are attached to hydrophobic sublayer(s) and there may be a great deal of penetration of the hydrogel polymer molecules into the hydrophobic sublayer(s). The polymer molecules of both layers are left in a state of inter-molecular mingling, especially in the region of the interface between the two layers. As a result of the inter-molecular mingling, water that is taken up in the hydrogel may find its way to the intersection between the substrate and the hydrophobic coating layer. The adhesion between the hydrophobic layer and the substrate is usually jeopardized by the moisture, and adhesive failure usually results. This process of moisture-induced adhesive failure is greatly exacerbated when the coating layers are thin.

Thin hydrophobic layers containing cellulose esters and acrylic polymers may be coated

directly on metal substrates, U.S. Pat. No. 5,001,009. Hydrogel coatings may be applied directly over such layers. Such systems perform well on coil type guide wires, because the coating is able to gain additional adhesion by penetrating between the coil wires. However, such layers tend to allow too much moisture penetration resulting in deterioration of adhesive bonds when applied onto mandril style metal substrates.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide materials which can be applied within layers directly on medical device surfaces on which it is difficult to achieve coating adhesion, and which allow layers to be applied over them to enhance performance and biocompatibility of such devices. It is another object of the present invention to provide methods for preparing such medical instruments.

It is a further object of the present invention to provide guide wires, catheters, drainage tubes, feeding tubes, and other devices which are used in contact with human tissues and fluids, with surfaces that show enhanced biocompatability and may become very lubricious when contacted by body fluids. It is another object to provide such devices which contain substances which combat infections, blood clots, inflammation, and other disorders that may result from in vitro placement and use of such medical devices.

According to a first aspect of the present invention, there is provided a medical device comprising a substrate having a surface to be coated. The surface is characterized as being relatively inert and does not have reactive functional groups on the surface. A polymer coating which may be a single or mixed (hybrid) polymer layer is provided on the substrate surface which is strongly bonded to the substrate surface. The polymer layer on the device surface is such that other layers applied over it will be strongly bonded to such layer.

Substrates to which coatings according to the invention may be applied include metals such as stainless steel, nickel, gold, chrome, nickel titanium alloy, platinum and others; plastics such as silicone, polyethylene, other polyolefins, polyesters, and others. Preferred devices include needles, guide wires, catheters, surgical instruments, equipment for endoscopy, wires, **stents,** angioplasty balloons, wound drains, arteriovenous shunts, gastroenteric tubes, urethral inserts, laparoscopic equipment, pellets, or implants. Particularly preferred embodiments include coated guide wires, particularly mandrel-type wires, catheters, drainage tubes, insulation in pacemaker leads, and smooth thin wires for coronary angioplasty or neurointervention or other procedures requiring a wire thickness of less than about 10-20 mils (250-500 microns).

According to a second aspect of the present invention, there are provided methods for preparing medical devices, comprising coating the medical device surface with a thin polymer layer of suitable composition such that the thin layer bonds well to the substrate surface, and such that succeeding coated layers will be strongly bonded to said thin polymer layer. The device is then coated with other layers designed to enhance performance and for biocompatibility of the medical device. Such layers may include medicated coatings which can serve as surface reservoirs for physiologically active agents to release efficacious concentrations of such agents near the device surface, hydrogel coatings to provide surface lubricity, color containing coatings, abrasion resistant coatings, combinations of one or more of the above, and other coatings intended to enhance the performance of the device.

This invention satisfies a long felt need for a thin well-bonded lubricious coating for indwelling medical devices. The invention succeeds where previous efforts at bonding surface layers to medical devices have failed, despite extensive efforts in a crowded and mature art. The invention eliminates the need for thick coatings, with enhanced performance. The materials and methods of the invention were not previously known or suggested, and their advantages were not previously appreciated. Further objectives and advantages that can be

attained by the present invention will become apparent from the detailed description.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In describing preferred embodiments of the present, specific terminology is employed for the sake of clarity. However, the invention is not intended to be limited to the specific terminology so selected, and it is to be understood that each specific element includes all technical equivalents which operate in a similar manner to accomplish a similar purpose.

Thin bond or tie coat layers according to the invention may be applied to difficult-to-bond-to substrates in order that other layers which cannot normally be bonded to such substrates may be satisfactorily bonded. The polymers of the invention are sufficiently resistant to degradation by solvents in succeeding layers that the coating does not lose adhesiveness when soaked in water and is impervious to water diffusion from the surface.

Classes of polymers which may be employed include acrylic polymers and copolymers based on monomers such as methylmethacrylate, butylmethacrylate, isobutylmethacrylate, ethylmethacrylate, methylacrylate, acrylic acid, styrene methacrylate, styrene acrylate, and others; vinyl polymers and copolymers such as polyvinylpyrrolidone, vinylpyrrolidone-vinylacetate copolymers, ethylene acrylic acid copolymers, epoxy polymers, and others. Exemplary commercial products that may be used in the invention include acrylics such as ARYLOID Registered TM (Rohm & Haas) AT-63, AT-51, AT-81, WR-97; Polyvinylpyrrolidone polyvinyl acetate copolymers such as PVP/VA (GAF) E-335, E-635; ethylene acrylic acid copolymers such as PRIMACOR TM (DOW) 5989, 5990; melamine resins such as CYMEL (CYTEC Industries) 303, 370, 380; epoxies such as EPON (Shell) 1001. Other appropriate polymers having the requisite characteristics will be apparent to persons of ordinary skill.

The polymers preferably, but not necessarily, contain reactive groups or points of reactivity such as hydroxyls, mono-, di- and tertiary amines, acids such as carboxyl, amides, or other groups which represent points of chemical reactivity. The polymers and points of chemical reactivity are able to form attractive forces such as hydrogen bonding toward the medical device surface, and also toward the coating layers to be applied over them. Such bonds are very strong, and prevent penetration of the top coat layer and water without requiring covalent or other ionic links between the device surfaces and the thin polymer tie coatings.

Polymers with reactive groups are preferred to help bond with substrates like metals. However, polymers lacking such groups such as acrylic or styrene polymers may also be used.

The reactive groups can also react to form a cross-linked matrix or help to form a cross-linked matrix. If desired, cross-linkers such as urea resins, melamines, isocyanates, phenolics, and others may be incorporated to cross-link the polymers of the invention with themselves, by reacting with the points of chemical reactivity on the polymer chains. Alternatively, cross-linkers may react with themselves to form a cross-linked matrix in which the tie coat polymers are enmeshed, resulting in a solvent-resistant layer. Cross-linking within the thin polymeric tie coats (either between the principal polymers or around them) is useful in promoting effective adhesion by ensuring that the solvents used in succeeding coating layers do not attack and degrade the tie coat polymer layer excessively and by resisting water penetration. When the tie coat layers are subjected to excessive solvent attack the polymer tie coat layer may be diluted by the succeeding coating layer thereby degrading the adhesive bond between the tie coat layer and the medical device surface. Excessive water penetration can also degrade adhesion.

Coatings according to the invention may be prepared with polymers that lack points of reactivity, such as acrylic or styrene polymers or copolymers. Likewise, coatings may be made without cross-linking. However, with such coatings a greater tie coat thickness may be

required or desirable than with layers made of polymers with points of reactivity and layers with cross-linking, in order to achieve a high degree of adhesion of succeeding layers according to the invention. For example, cross-linked coatings with polymers having reactive groups may be about two to about ten microns thick, in contrast with a coating as in Example 1, where a water-borne acrylic styrene copolymer is applied to metal, with a hydrogel layer on top, and a total thickness of about 30-40 microns.

The tie coat layers of the present invention are extremely durable, even when immersed in water for prolonged periods. As will be shown in examples, coatings on stainless steel can be soaked in water for months without losing adhesion, even when hydrogel layers are applied to the samples. Hydrogel layers typically absorb several times their weight in water and serve as a pathway for water diffusion into the layer (s) between the hydrogel layer and the medical device surface. Such exposure to water, especially for extended periods represents a considerable challenge to the tie coats of the present invention and the fact that they are able to endure such challenges without adhesive failure is a surprising result. The tie coat layers of the present invention are so thin, typically less than 5 microns, that the adhesiveness is all the more remarkable.

The coatings of the invention may be thin, on the order of 0.0002"-0.0005" (5-12 microns), although it may be as thick as is desirable. Preferably, the coating is in the range of about 2 to about 100 microns, more preferably less than about 80 microns, or 60 microns, and particularly preferred embodiments are less than about 15 microns thick. Bond coats of about 2 to about 10 microns are generally quite adequate. If the coating is thicker, it may cause other problems in certain applications where thinness is important.

A coating according to the invention may include a bond coat of about 5 microns and a two-layer hydrogel comprising a 5 micron base coat and a 5 micron top coat, with a total thickness of about 15 microns.

Examples of substrates and bond coat formulations that are effective with them are listed below. Many other combinations will be apparent to a person of ordinary skill following the teachings of the invention.

stainless steel:	epoxy resin; vinylpyrrolidone-vinyl acetate copolymer; styrene acrylic aqueous dispersion; ethylene acrylic acid copolymer plus melamine resin; ethylene acrylic acid copolymer plus melamine resin plus hydroxyl function acrylic polymer plus isocyanate polymer; carboxyl function acrylic polymer plus epoxy resin; acrylic dispersion polymer
poly-ethylene	ethylene acrylic acid copolymer plus melamine resin plus hydroxyl function acrylic polymer plus isocyanate polymer
silicone	ethylene acrylic acid copolymer plus melamine resin plus hydroxyl function acrylic polymer plus isocyanate polymer plus oxygen plasma
polyester	ethylene acrylic acid copolymer plus melamine resin plus hydroxyl function acrylic polymer plus isocyanate polymer
polyamide	oxygen plasma plus polyvinylbutynal

The coatings are coherent in that they form a continuous surface layer. When coated with a top coat, the resulting coatings are resistant to removal on prolonged soaking in aqueous fluids, and are adherent to a wide variety of substrates.

There are several useful tests of adhesion of coatings comprising the bond coat of the invention. Two of them are the dry adhesion tape test and the wet rub test. Uncovered tie coat coatings generally adhere well to a substrate, as do tie coat coatings with a base coat such as a cellulose ester layer, but problems frequently arise when a surface coating is applied, such as a hydrogel. Completed coatings according to the invention are able to endure immersion in water for at least an hour and remain adhesive and resistant to removal by abrasion as indicated by the wet rub test, and, after drying, the tape test. This sets them apart from the prior art.

In the wet rub test, parallel cuts are made through the coating with a razor or knife. The coating is immersed in water for a predetermined period, such as an hour. A finger is then rubbed briskly across the cuts. Peel-back of the coating constitutes coating failure. In the dry adhesion test, adhesive tape is pressed firmly onto the coating, then peeled off briskly. Removal of the coating constitutes failure.

The coatings according to the invention may be applied to the surface of a biomedical device or other device with sufficient thickness and permanence to retain the coating's desirable qualities throughout the useful life of the coated device. They have sufficient thinness to be useful in many applications inappropriate for prior art coatings. The coatings of the invention are nonreactive with living tissue and are non-thrombogenic in blood.

The coatings may be applied by various techniques such as dip, spray, brush, wipe, or other methods known to those skilled in the art. The coating solutions have low viscosities, typically less than 100 CPS, and have good spreading properties. The coatings are baked at elevated temperatures, typically 50o C. to 100o C., to drive off the organic solvents.

Gas plasma treatment may be done according to conventional methods. A vacuum is drawn, a gas such as oxygen or ammonia is allowed in, it is excited with Rf, and the surface is allowed to stay in contact with the resulting plasma for a sufficient time, such as 20 minutes, to put functional groups on the surface. Oxygen produces hydroxyl surface groups, and ammonia produces amine groups covalently bound to the polymer surface. Over time the groups tend to fold into the surface and become less reactive, so plasma-treated surfaces are best used fresh.

DETDESC:
The coating systems described herein produce coatings that remain bonded in aqueous fluids on surfaces such as polyethylene, polypropylene, polyamide, polyester, silicone and metals such as stainless steel, platinum, gold, nickel, titanium, nickel-titanium alloys, chrome and other surfaces that are generally considered as presenting adherence problems. It may be necessary to treat some surfaces with gas plasma or other ionizing treatment to promote adhesion to the substrates. The following examples show some embodiments of how the invention can be used.

EXAMPLE 1

A stainless steel surface was brush coated with the following solution, and dried for 30 minutes at 85o C. Add in order, stir until dissolved.

Epoxy resin	5.55 gm
Xylene	2.37 gm
Tetrahydrofuran (THF)	62.08 gm
Cyclohexanone	10.0 gm
Ethanol	2.5 gm
Vinylpyrrolidone-vinylacetate copolymer	2.5 gm

The coating was tested for adhesion by cutting lines through it with a knife and then rubbing briskly across the cuts with a finger after the coating was immersed in water. No failure of adhesion (i.e. peel back) occurred after the wet rub test. Next, the coating dry adhesion was tested by pressing Universal Tape 83436 tape (United Stationers Supply, Co.) firmly onto the coating and peeling the tape off briskly. No coating should be removed by this test. This sample showed no adhesion failure on the tape test.

EXAMPLE 2

A styrene acrylic aqueous dispersion polymer (55% solids) was brush coated on a stainless steel surface, and dried for 30 minutes at 85o C. This coating showed excellent adhesion when tested according to example 1.

EXAMPLE 3

A sample as per example 2 was overcoated with a hydrogel composition consisting of:

Polyvinyl pyrrolidone (PVP)	9.4 gm
Ethanol	136.1 gm
Butyrolactone	30.6 gm
0.0625% nitrocellulose in cyclohexanone	3.8 gm

The coating was dried for 25 hours at 85o C. The coating passed the wet and dry adhesion tests according to example 1.

EXAMPLE 4

The following solution was brush coated on a stainless steel surface, and dried at 85o C. for 2 hours.

5% (w/w) Ethylene acrylic acid copolymer in tetrahydrofuran (THF)	15 gm
Cyclohexanone	2 gm
Melamine resin	.24 gm
Xylene	.23 gm
Butanol	.07 gm
Trichloroacetic acid	.1 gm

This coating was dried for 15 hours at 85o C. The adhesion of the coating was tested according to example 1, and had good adhesion under both wet and dry conditions.

EXAMPLE 5

A sample as per example 4 was overcoated with the following solution and dried 2 hours at 85o C.

Nitrocellulose solution*	170.6 gm
Cyclohexanone	88.0 gm
Benzyl alcohol	48.0 gm
10% (w/w) polyurethane in THF	86.0 gm
Acrylic polymer with hydroxyl function	18.0 gm
Melamine resin	4.5 gm
Xylene	17.55 gm
Butanol	4.95 gm
Trichloracetic acid	0.5 gm

*Nitrocellulose solution:	*
1/4" RS Nitrocellulose	687 gm
Butyl acetate	459 gm
Toluene	360 gm
Ethyl acetate	894 gm
Camphor	132 gm
Dibutylphthalate	180 gm

Next the sample was overcoated with the following hydrogel solution and dried for four hours at 85o C.

PVP	9.4 gm
Ethanol	136.1 gm
Butyrolactone	30.6 gm
0.0625% Nitrocellulose solution in cyclohexanone	3.8 gm

The adhesion of the coatings was tested according to example 1 and had good adhesion under both wet and dry conditions. The sample had good wet lubricity. If the first coating was omitted the adhesion failed under the test condition.

EXAMPLE 6

The following solution was dip coated on a stainless steel wire and dried for 2 hours at 85o C.

5% (w/w) ethylene acrylic acid copolymer in THF	15 gm
Cyclohexanone	4 gm
Hydroxyl function acrylic polymer	.24 gm
Melamine resin	.06 gm
80% (w/w) isocyanate polymer in THF	.32 gm
Trichloroacetic acid	.20 gm

Next the sample was overcoated with the same two overcoating solutions per example 5. The

adhesion was good when tested according to example 1 under wet and dry conditions. The sample continued to show good adhesion after soaking in water for more than 130 days. The coating had good wet lubricity.

EXAMPLE 7

Polyethylene tubing was exposed to oxygen plasma treatment. The PE tube was then coated with the same coatings as per example 6. The adhesion was good when tested according to example 1 under wet and dry conditions. The sample had good wet lubricity.

EXAMPLE 8

Polyethylene tubing was treated as in example 7, except that the middle coating just underneath the hydrogel consisted of:

1/4" RS Nitrocellulose	2.89 gm
Dibutylphthalate	1.1 gm
Camphor	.8 gm
Polyurethane	6.8 gm
Cyclohexanone	28.3 gm
Methylethylketone	1.6 gm
Benzyl alcohol	7.1 gm
THF	10.1 gm
Ethylacetate	2.3 gm
Ethanol	14.7 gm
Isopropanol	5.5 gm
Toluene	22.9 gm
Butylacetate	1.3 gm

The sample had good adhesion when tested according to example 1 under both wet and dry conditions, and had good wet lubricity.

EXAMPLE 9

Silicone tubing was treated as in example 8. The coating had good adhesion when tested according to example 1 under wet and dry conditions, and the coating had good wet lubricity.

EXAMPLE 10

Silicone tubing was exposed to oxygen plasma treatment by placing in an evacuated vessel and subjecting to alternate cycles of adding oxygen and cycling Rf power. Initially, oxygen is fed in at 550 +/- 50 mTorr for 0.25 minutes. The oxygen is turned off, and the Rf power is turned on, with 450 +/- 50 watts forward and </= 50 watts reverse, for 2 minutes. These two steps are repeated five times, with the remaining oxygen cycles lasting 2 minutes. The tie coat is typically applied to the plasma treated surface before degradation of the plasma treatment, within a day or two.

Next, the treated tubing was dip coated with the following solutions and dried one hour at 85o C.

Polyvinylbutyral	18.0 gm
Ethanol	35.4 gm
Xylene	34.9 gm
Methylethyl ketone	43.4 gm
Propylene glycol methyl ether acetate	48.9 gm
Dipropylene glycol methyl ether acetate	9.0 gm
Isobutyl acetate	1.89 gm

This coating was overcoated with the same hydrogel as used in example 3. The coated sample had good adhesion when tested according to example 1 under both wet and dry conditions, and had good wet lubricity.

EXAMPLE 11

Stainless steel was coated with the following solution and dried 60 minutes at 85o C.

Polyvinyl butyral	9.00 gm
Ethanol	17.70 gm
Xylene	18.19 gm
Methylethylketone	21.70 gm
Propylene glycol methyl ether acetate	24.45 gm
Dipropylene glycol methyl ether acetate	4.50 gm
Isobutyl acetate	.90 gm
Acrylic polymer with hydroxyl function	1.52 gm
Melamine resin	.38 gm
Butanol	.42 gm

Next, the sample was overcoated with the last two coatings that were used to overcoat the first coating in example 5. The sample had good adhesion when tested according to example 1 under wet and dry conditions, and the sample had good lubricity.

EXAMPLE 12

A sample of polyester tubing was treated as per example 8. The sample had good adhesion when tested according to example 1 under wet and dry conditions, and the sample had good wet lubricity.

EXAMPLE 13

A stainless steel surface was dip coated with the following tie coat solution and dried 2 hours at 85o C.

Carboxyl function acrylic polymer	1.85 gm
Aromatic 150	2.32 gm
Butyl Cellosolve	.33 gm
THF	3.55 gm
Xylene	.13 gm
Epoxy resin	.39 gm

Next, the sample was overcoated with the same hydrogel coating as per example 3, and dried for 2 hours at 85o C. The sample had good adhesion when tested according to example 1 under wet and dry conditions, and had good lubricity.

EXAMPLE 14

A sample of stainless steel was dip coated with the same tie coat solution as used in example 1, and was then dried for 2 hours at 85o C. Next, the sample was overcoated with the last two coatings of example 5. The sample had good adhesion when tested according to Example 1 under wet and dry conditions, and the sample had good lubricity when wet.

EXAMPLE 15

A sample of stainless steel was dip coated with the following tie coat composition, and was dried for 2 hours at 85o C.

Water	8 gm
10% Triton x 100 nonionic surfactant	.88 gm
50% Acrylic dispersion polymer	18.8 gm

Next, the sample was overcoated with the last two coatings of example 5. The sample had good adhesion when tested according to example 1 under wet and dry conditions, and the sample had good lubricity when wet.

EXAMPLE 16

A sample of PEBAX polyamide tubing was treated according to Example 10. The sample had good adhesion when tested according to Example 1 under wet and dry conditions, and had good wet lubricity.

EXAMPLE 17

A sample of Nylon 12 tubing was treated as in Example 16, except that no oxygen plasma treatment was used. The sample had good adhesion when tested according to Example 1 under wet and dry conditions, and had good wet lubricity.

The embodiments illustrated and discussed in this specification are intended only to teach those skilled in the art the best way known to the inventors to make and use the invention. Nothing in this specification should be considered as limiting the scope of the present

invention. Modifications and variations of the above-described embodiments of the invention are possible without departing from the invention, as appreciated by those skilled in the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described.

CLAIMS: What is claimed is:

[*1] 1. An insertable medical device comprising an inert surface of the device that does not have reactive functional groups, the inert surface being modified by a biocompatible surface coating, the surface coating comprising:

(a) a coherent bond coat layer applied to the inert surface with a thickness below about 100 microns such that the bond coat layerdoes not penetrate into the device, the bond coat layer comprising at least one bonding polymer bonded with non-covalent bonds with the inert surface of the device, wherein the bond coat layer comprises a cross-linked matrix, and further comprising

(b) an outer layer applied to the bond coat layer that adheres to the bond coat layer, the coating remaining adherent to the surface and resistant to abrasion and to removal from the device after soaking in water relative to a coating without the bond coat layer.

[*2] 2. A device according to claim 1, in which the bonding polymer is selected from the group consisting of acetals, ethylene copolymers, polymers containing hydroxyl, amine, carboxyl, or amide reactive groups, styrene acrylic polymer, ethylene acrylic acid copolymer, carboxyl function acrylic polymer, hydroxyl function acrylic polymer, acrylic dispersion polymers, methylmethacrylate, butylmethacrylate, isobutylmethacrylate, ethylmethacrylate, methylacrylate, ethylacrylate, acrylic acid, styrene methacrylate, and styrene acrylate, polyvinylpyrrolidone, vinylpyrrolidone-vinylacetate copolymers, ethylene acrylic acid copolymers, epoxy polymers, and copolymers thereof.

[*3] 3. A device according to claim 1, wherein the bonding polymer includes reactive groups.

[*4] 4. A device according to claim 3, in which the cross-linked matrix comprises a cross linker that interacts with the reactive groups of the bonding polymer, the cross linker being selected from the group consisting of urea resins, melamines, isocyanates, epoxies, and phenolics.

[*5] 5. A device according to claim 1, in which the bond coat thickness is between about 1 and about 10 microns.

[*6] 6. A device according to claim 1, in which the surface coating has a total coating thickness less than about 40 microns.

[*7] 7. A device according to claim 1, in which the inert surface comprises a material selected from the group consisting of stainless steel, nickel, gold, chrome, nickel titanium alloy, platinum, metals, silicone, and polyesters.

[*8] 8. A device according to claim 1, selected from the group consisting of needles, guide wires, catheters, surgical instruments, equipment for endoscopy, wires, **stents,** angioplasty balloons,wound drains, arteriovenous shunts, gastroenteric tubes, urethral inserts, laparoscopic equipment, pellets, and implants.

[*9] 9. A device according to claim 1 in which the outer layer comprises at least one of a lubricious coating, a medicated coating, a colored coating, an abrasion-resistant coating.

[*10] 10. A device according to claim 1, the inert surface having been pretreated by gas plasma or other ionizing treatment to put functional groups on the inert surface, to which the bonding polymer bonds non-covalently.

[*11] 11. The device of claim 1, the bond coat layer having been formed with cross linker that interacts with reactive groups of the bonding polymers.

[*12] 12. The device of claim 1 further comprising a surfactant in the bonding layer.

[*13] 13. A device according to claim 1, further comprising covalent bonds between the bond coat layer and the surface of the device.

[*14] 14. A device according to claim 1, wherein the coating is resistant to removal by adhesive tape after the soaking.

[*15] 15. A device according to claim 1, the bond coat layer and the outer layer having an interface where the components of the layers are interpenetrated.

[*16] 16. In a biocompatible coating comprising an outer layer on an insertable medical device having an inert surface without reactive functional groups, the improvement comprising a coherent bond coat layer formed by a bonding polymer that bonds non-covalently with the inert surface of the device without penetrating into the surface, wherein the bond coat layer comprises a cross-inked matrix, the bonding polymer flirter adhering to an outer layer applied over the bond coat layer, and the coating remaining adherent to the substrate and resistant to abrasion and removal during a period of insertion relative to a coating without the bond coat layer.

[*17] 17. The device of claim 11, wherein the cross linker is selected from the group consisting of urea resins, melamines, isocyanates, epoxies, and phenolics.

[*18] 18. The device of claim 1, wherein the bonding polymer is selected from the group consisting of acrylics, vinyl polymers, polymers having reactive groups, and copolymers thereof.

[*19] 19. The device of claim 1, wherein the insertabe device is selected from the group consisting of surgical instruments, endoscopic equipment, laparoscopic equipment, pellets, and implants.

[*20] 20. The device of claim 1, wherein the coating is applied without subjecting the coating to heating for more than about six hours.

[*21] 21. The device of claim 1, wherein the outer layer is hydrophilic and the bond coat layer resists penetration of water to the surface of the device.

[*22] 22. The device of claim 1, wherein the outer layer is comprised of a plurality of layers.

[*23] 23. An insertable medical device comprising a surface and a biocompatible surface coating comprising a first bond coat layer on the surface, and a second outer layer on the bond coat layer, the bond coat layer comprising a bonding polymer having reactive functional groups which form a non-covalent adhesive bond to the surface and to the outer layer, wherein the bond coat layer comprises a cross-linked matrix, the bond coat layer further not penetrating into the surface, the bond coat layer preventing penetration of water to the surface, and the coating remaining adherent to the surface and resistant to abrasion and to removal from the device after soaking in water relative to a coating without the bond coat layer.

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p. 11
— plasma activate surface
RF or corona

*Pat. No. 6248811, **

6,248,811

incomplete

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June 19, 2001

Bioactive **surface** coating

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CORE TERMS: coating, polymer, monomer, substrate, acid, mol, film, adhesion, solvent, coated, salt, ratio, cell, methacrylate, bacteria, radiation, bacterial, minute, molar, independently, grafting, carboxyl, formula, dimethyl sulfoxide, activated, cinnamoylethyl, advantageously, antibacterial, carboxylate, dissolved

ABST:
A process is disclosed for preparing bioactive, covalently fixed coatings on the surfaces of substrates, by grafting to a surface of the substrate a coating polymer which contains the following monomers in copolymerized form:

(i) at least one monomer of the general formula:

R-(A)<a> (I),

in which

R is a mono- or diolefinically unsaturated organic radical having a valence a,

A is a carboxyl group, a sulfuric acid group, a sulfonic acid group, a phosphoric acid group, a phosphonic acid group, a phosphorous acid group, a phenolic hydroxyl group, or a salt of one of these acid groups, and

a is 1, 2 or 3; and

(ii) at least one monomer which is sensitive to UV radiation.

NO-OF-CLAIMS: 16

EXMPL-CLAIM: 1

NO-OF-FIGURES: 7

NO-DRWNG-PP: 4

SUM:

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a process for coating surfaces, preferably polymer substrates, with coating polymers, which owing to the presence of specific functional groups, are fixed bioactively and covalently, i.e., permanently, on the surfaces. The coatings are anti-bacterial and can, moreover, be formulated so as to inhibit or promote cell proliferation thereon. The invention also relates to articles having surfaces coated in this way for, inter alia, medical or biotechnical purposes.

2. Description of the Background

The colonization and multiplication of bacteria on surfaces is a phenomenon which is in general unwanted and is frequently associated with disadvantageous consequences. For instance, in the drinking water and beverage industry bacterial populations may lead to health hazards. Bacteria on or in packaging frequently cause food contamination, or even infections in the consumer. In biotechnical plants that are to be operated under sterile conditions, bacteria alien to the system constitute a considerable processing risk. Such bacteria may be introduced with raw materials or may remain in all parts of the plant if sterilization is inadequate. By means of adhesion, sections of the bacterial population may escape the normal liquid exchange entailed in rinsing and cleaning and can multiply within the system.

Bacterial colonies are also known in water treatment plants (for example for membrane desalination) or else in containers which are filled with dissolved or liquid undiluted organic substances and which have advantageous conditions for bacterial populations. Such microbial colonization can, to a considerable extent, lead to the blocking and/or corrosive destruction of the plant.

Particular importance is attached to protecting against bacterial adhesion and propagation in nutrition, in human care, especially in the care of the elderly, and in medicine. In the case of large-scale outlets serving food or drinks there are considerable risks especially when, rather than using disposable tableware with its attendant problem of waste, reusable tableware is employed that is not adequately cleaned. Also known is the harmful propagation of bacteria in hoses and pipes which conduct foods, as is their multiplication in storage containers and in textiles in a hot and damp environment, for example in swimming baths. Facilities of this kind are preferred habitats for bacteria, as are certain surfaces in areas through which many people pass, for example in public transport vehicles, hospitals, telephone boxes and schools and, especially, in public toilets.

In the care of the sick and elderly, the often reduced defenses of the those affected necessitate careful measures to counter infections, especially in intensive care wards and in the case of care at home.

Particular care is required in the use of medical articles and instruments in the case of medical investigations, treatments and interventions, especially when such instruments or articles come into contact with living tissue or with body fluids. In the case of long-term or permanent contact, especially in the case of implants, catheters, **stents,** cardiac valves and pacemakers, bacterial contamination can become a life-threatening risk to the patient.

Diverse attempts have already been made to suppress the colonization and propagation of bacteria on surfaces. In J. Microbiol. Chemoth. 31 (1993), 261-271 S. E. Tebbs and T. S. J. Elliot describe paint-like coatings with quaternary ammonium salts as antimicrobial components. It is known that these salts are dissolved out of the coating material by water, by aqueous or other polar media and by body fluids, and that their action is therefore short-lived. This applies equally to the incorporation of silver salts in coatings, as described in WO 92/18098.

T. Ouchi and Y. Ohya in Progr. Polym. Sci. 20 (1995), 211 ff., describe the immobilization of bactericidal active substances on polymer surfaces by means of covalent bonding or ionic interaction. In such cases, the microbicidal actions are frequently reduced markedly relative to the pure active substance. Heteropolar bonds often prove to be of insufficient stability. Furthermore, the killing of the microbes leads in general to unwanted deposits on the surfaces, which mask the subsequent bactericidal action and form the basis for a subsequent bacterial colonization.

W. Kohnen et al. in ZB1. Bakt. Suppl. 26, Gustav Fischer Verlag, Stuttgart-Jena-New York, 1994, pages 408 to 410, report that the adhesion of Streptococcus epidermidis on a polyurethane film is reduced if the film is pretreated by glow discharge in the presence of oxygen and is then grafted with acrylic acid.

In many medical applications it is not only important that the surfaces be kept free from bacteria; rather, colonization with cells also has a part to play. In modern medicine frequent use is made of exogenous articles in such a way that they come into medium- or long-term contact with tissue or body fluids. Examples are implants, such as pacemakers, **stents** and prostheses, and also suture materials, drainage hoses and catheters. Such articles may consist, inter alia, of metals, ceramic and/or polymers. These materials must be biocompatible, i.e., compatible with the tissue and/or with the tissue fluids with which they are in contact. Numerous processes have been disclosed which are intended to make polymers biocompatible or to improve their biocompatibility. One of these methods is the colonization of the polymer surfaces with human cells.

On the other hand, there are medical applications where colonization of the surface of such exogenous articles with human cells is extremely undesirable. For instance, cell colonization in the case of catheters applied intracorporally in the medium term (indwelling catheters) is just as harmful as in the case of cardiac valves or **stents** which are implanted for the long

term. WO 94/16648 describes a process by means of which it is intended to prevent the adhesion and proliferation of cells on the surface of implanted eye lenses made from polymer material. According to EP 0 431 213, polymers are equipped with cell-repelling properties by rendering their surface hydrophilic using strong mineral acids. This leads to a reduction in the cell adhesion.

The subsequent chemical modification of polymer surfaces, however, is usually not uniform. In many cases there remain areas which have not been treated, or not sufficiently treated, which form starting points for cell colonization. Furthermore, the cell-repelling properties of the treated surfaces are in many cases not persistent.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide an improved process for the bioactive coating of surfaces by means of which surfaces can be kept substantially and persistently free from bacteria, for example cocci, in a physiologically compatible manner without thereby altering the mechanical properties of the treated materials or giving rise to any other of the disadvantages of the methods described above.

It is another object of the present invention to provide a process by means of which the antibacterial coatings may be formulated to additionally either inhibit or promote cell proliferation.

It has surprisingly been found that antibacterial, covalently fixed coatings may be prepared advantageously on the surface of substrates, especially polymer substrates, by grafting to a surface of a substrate a coating polymer which comprises, in copolymerized form,

(i) at least one monomer of the general formula (I):

R-(A)<a>

in which R is a mono- or diolefinically unsaturated organic radical having the valence a,

A is a carboxyl group (-COOH), sulfuric acid group (-OSO<2>OH), sulfonic acid group (-SO<3>H), phosphoric acid group (-OPO(OH)<2>), phosphonic acid group (-PO(OH)<2>), phosphorous acid group (-OP(OH)<2>), a phenolic hydroxyl group, or a salt of one of these groups, and

a is 1, 2 or 3; and

(ii) at least one monomer which is sensitive to UV radiation.

A more complete appreciation of the invention and many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings.

DRWDESC:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1. Reduction in adhesion of Staphylococcus aureus on films coated in accordance with the invention, as a function of the molar COO< -> /SO<3>< -> ratio

FIG. 2. Reduction in adhesion of Staphylococcus epidermidis on films coated in accordance with the invention, as a function of the molar COO< -> /SO<3>< -> ratio

FIG. 3. Reduction in adhesion of Staphylococcus pyogenes on films coated in accordance with

the invention, as a function of the molar COO< -> /SO<3>< -> ratio

FIG. 4. Reduction in adhesion of Klebsielia pneumoniae on films coated in accordance with the invention, as a function of the molar COO< -> /SO<3>< -> ratio

FIG. 5. Reduction in adhesion of Pseudomonas aeruginosa on films coated in accordance with the invention, as a function of the molar COO< -> /SO<3>< -> ratio

FIG. 6. Reduction in adhesion of Escherichia coli on films coated in accordance with the invention, as a function of the molar COO< -> /SO<3>< -> ratio

FIG. 7. Reduction in cell growth of human fibroblasts on coated films, as a function of the molar COO< - ->/SO<3>< -> ratio

DETDESC:

DETAILED DESCRIPTION OF THE INVENTION

The organic radical R may have a hydrocarbon structure, or may comprise additional atoms in addition to carbon and hydrogen, for example oxygen, nitrogen and/or silicon atoms. R may be a radical of a phenolic compound. Preferably, R has 2 to 20 carbon atoms, more preferably 2 to 10 carbon atoms.

When the coating polymer comprises a monomer I having a carboxyl group or a salt of the carboxyl group (i.e., a carboxylate group) then, preferably, either this monomer has at least one further radical A which is not a carboxyl group or a carboxylate group, or the coating polymer having at least one additional monomer I in which A is not a carboxyl group or a carboxylate group. In this way, the relatively weak antibacterial action of the carboxyl group or a salt thereof may be intensified.

Among the salts of groups specified for A, preference is given to the alkali metal salts and, in particular, to sodium salts. A common feature of the monomers of the formula I is that they have 1 or 2 olefinic double bonds and also at least one acidic group or a salt of an acidic group.

Coatings produced on various substrates by plasma-induced graft polymerization are known, for example, from B. Lassen et al., Clinical Materials 11 (1992), pages 99-103, and have been investigated for biocompatibility. In that case, however, only monomers sensitive to UV radiation were grafted, and no mention is made of grafting onto activated substrate surfaces. Moreover, plasma is not an optimal polymerization initiator. H. Yasuda refers accordingly, in J. Polym. Sci.: Macromolecular Review, Vol. 16 (1981), 199-293, to the undefined and uncontrollable chemistry of plasma polymerization. This may be acceptable for some purposes, but is problematic for medical and biotechnical applications, for the precise reason that a special criterion here is reproducible coatings of consistently high quality.

The surfaces modified in accordance with the invention may reduce the adhesion of bacteria to a high extent even over a prolonged period. The bacterial strains whose adhesion is reduced or prevented in accordance with the invention include, for example, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, and Enterobacter faecium. The coated surfaces are free from migratable and/or extractable monomer and oligomer components. Unwanted side effects resulting from released exogenous substances or from dead bacteria may be avoided from the outset. The surfaces of the grafted-on coatings are therefore of outstanding physiological compatibility. The particular conditions under which the surfaces, in addition to their properties of bacterial inhibition, have a cell proliferation-inhibiting or -promoting effect will be discussed below.

In the process according to the invention the optionally activated substrate surfaces are first coated with the coating polymers, and the coating may then be fixed covalently, i.e., permanently, to the substrate surface by gentle grafting of the ready-formed coating polymer under the action of UV radiation.

1. The Coating Polymers

The coating polymers have at least one copolymerized monomer of the general formula I whose functional group A is responsible for the bioactive (i.e., antibacterial) properties of the polymeric coating. These monomers I include monomers of the general formulae II and III:

(C<n>H<2n - q - x>)(COOR<1>)<x> Formula II

(C<n>H<2n - q - x>)(SO<3>R<1>)<x> Formula III

which are preferred monomers for the preparation of the coating polymers. Coating polymers which contain not only at least one monomer II but also at least one monomer III have a particularly strong antibacterial action, it being possible for the radicals (C<n>H<2n - q - x>) to be identical or different. In the formulae II and III:

n independently at each occurrence is an integer from 2 up to and including 6;

x independently at each occurrence is 1 or 2;

q independently at each occurrence is 0 or 2, and

the radical R<1>, independently at each occurrence, is-H or an equivalent of a metal ion, advantageously an alkali metal ion and, in particular, a sodium ion.

In accordance with the definitions given, the radical (C<n>H<2n - q - x>) independently at each occurrence is a straight-chain or branched monovalent alkenyl radical (q = 0, x = 1) or alkadienyl radical (q = 2, x = 1) or a divalent alkenylene radical (q = 0, x = 2) or alkadienylene radical (q = 2, x = 2).

Instead of two monomers II and III it is also possible to employ only one monomer (II + III) which contains the COOR<1> and SO<3>R<1> groups in the same molecule.

In addition, benzene-derived monomer components of the formula IV

(C<6>H<6 - b - c - d>)B<b>R<3><c>(OH)<d> Formula IV

are within the scope of formula I and can be present advantageously as monomers in the coating polymer, where

B independently at each occurrence is a mono- or diolefinically unsaturated straight-chain or branched radical of the formula (C<n>H<2n - 1 - q - x>)(COOR<1>)<x> or-(C<n>H<2n - 1 - q - x>)(SO<3>R<1>)<x>, in which R<1>, n, q and x are as defined above.

R<3> independently at each occurrence is C<1-4>-alkyl,-NH<2>,-COOH,-SO<3>H,-OSO<3>H,-OPO(OH)<2>,-PO(OH)<2>,-OP(OH)<2>,-PO(O< ->)OCH<2>CH<2>N< +> (CH<3>)<3>,-PO(O< ->)OCH<2>CH<2>N< +> (CH<3>)<3>,-OP(O-CH<2>CH<2>N< +> (CH<3>)<3>, or a salt thereof, preferably an alkali metal and, more preferably, a sodium salt;

b is 1, 2 or 3;

c is 0, 1, 2 or 3; and

d is 0, 1, 2 or 3;

with the proviso that b + c + d is [less than or equal to] 6, advantageously [less than or equal to] 4.

Other suitable monomers for preparing the coating polymers which are grafted onto the activated substrate surface are, in accordance with the formula I, olefinically unsaturated, acidic sulfuric esters and their salts; sulfonic acids and their salts; phosphonic acids and their neutral or acidic salts; phosphoric esters and their neutral or acidic salts; and phosphorous esters and their neutral or acidic salts. Finally, mention may also be made of phenols having a functionality (or basicity) of from 1 to 3 and containing olefinic groups, and also their salts, corresponding to the formula I, as suitable monomers.

The coating polymers can, of course, in every case, and not only as in the above-mentioned case of the monomers II and III, contain different A radicals, which is achieved through an appropriate choice of monomers having different A radicals.

Of the monomers of the general formulae I to IV which are suitable for preparing the coating polymers and which comprise one or more identical or different radicals A in the molecule, mention may be made, by way of non-limiting example, of acrylic acid, methacrylic acid, 4-vinylsalicylic acid, itaconic acid, vinylacetic acid, cinnamic acid, 4-vinylbenzoic acid, 2-vinylbenzoic acid, sorbic acid, caffeic acid, maleic acid, methylmaleic acid, dimethylmaleic acid, dihydroxymaleic acid, isocrotonic acid, fumaric acid, methylfumaric acid, allylacetic acid and the alkali metal salts, especially the sodium salts, of these acids; vinylsulfonic acid, allylsulfonic acid, methallylsulfonic acid, 4-styrenesulfonic acid, 2-styrenesulfonic acid, vinyltoluenesulfonic acid, 4-carboxy styrenesulfonic acid and the alkali metal salts and especially the sodium salts of these sulfonic acids; diprimary 1,3-butadiene-1,4-diol diphosphate, 4- and 2-vinylphenol, 2-allylhydroquinone and 4-vinylresorcinol, and the corresponding salts.

In addition to the monomers of the general formulae I to IV it is also possible for other monomers to be present in the coating polymer which may make little or no contribution to the bioactive properties of the coating. Examples of these monomers include, for example, vinyl ethers, such as vinyl methyl ether and vinyl butyl ether; vinyl esters, such as vinyl acetate and vinyl propionate; vinyl ketones, such as vinyl ethyl ketone and vinyl n-butyl ketone; nitriles, such as acrylonitrile and methacrylonitrile; carboxamides, such as acrylamide, N,N-dimethylacrylamide and methacrylamide; carboxylic anhydrides, such as maleic anhydride; carboxylic esters, such as methyl acrylate, ethyl acrylate, 2-ethyl hexyl acrylate, methyl methacrylate, 2-hydroxy ethyl acrylate, 2-(2'-hydroxyethoxy)ethyl acrylate, 2-hydroxy-1-methyl ethyl acrylate, 2-N,N-dimethylamino ethyl acrylate, npropyl methacrylate, 2-hydroxy ethyl methacrylate, 2-(2'-hydroxyethoxy)ethyl methacrylate, 2-hydroxy-1-methyl ethyl methacrylate, 2-N,N-dimethylamino ethyl methacrylate, diethylene glycol methacrylate, triethylene glycol diacrylate, ethyl vinylsulfonate and 2-hydroxyethyl vinylsulfonate; olefins and diolefins, such as 1-butene, 1-hexene, 1-octene, 1,3-butadiene, isoprene and chloroprene; vinylsiloxanes and other silicon-containing vinyl monomers, such as tris(trimethylsiloxy)methacryloyl-propylsilane and tris(trimethylsiloxy)acryloylpropylsilane. These or other monomers may even be present in the predominant amount, for example up to 90 mol-%. Accordingly, these other monomers may comprise 0 to 90% mol % of the total monomers used in the polymer. This range includes all specific values and subranges therebetween, including 5, 10, 25, 50, and 75 mol %.

Monomers having groups which can be converted into groups A may be regarded as potential monomers of the formula I. They include primarily esters, anhydrides, acid amides and nitrites which can be hydrolyzed at least on the surface-and it is only this which is important in terms of bioactive properties-in a known manner using acid or alkali to give carboxyl or

carboxylate groups or sulfonic acid or sulfonate groups, respectively. For as long as this is not taking place, these monomers are regarded as additional, non-bioactive monomers within the meaning of the present invention.

Preferred coating polymers contain in copolymerized form (a) monomers with carboxylic acid and/or carboxylate groups and (b) monomers with sulfonic acid and/or sulfonate groups. The molar proportions of these monomers in the coating polymers together being generally from 5 to 40%, advantageously from 5 to 30% and, in particular, from 15 to 20%. These ranges include all specific values and subranges therebetween, including 10, 25, and 35 mol %.

The molar ratio of the monomers (a) to the monomers (b) is advantageously < 10, especially < 5. Pronounced anti-bacterial properties are shown by coating polymers in which this ratio is from 0.5 to 10, advantageously from 0.5 to 5. If the ratio is in the range from 0.4 to 3, advantageously from 0.4 to 2, the coating polymers show not only the antibacterial action but also strong cell proliferation-inhibiting properties. If the ratio is in the range from 2 to 10, advantageously from > 3 to 5, the coating polymers, surprisingly, have cell proliferation-promoting properties. A coating inhibits cell proliferation, in the sense of the invention, when the adhesion and multiplication of mammalian cells on the coating is reduced relative to the uncoated substrate. The coating is regarded as being cell proliferation-promoting within the context of the invention if the adhesion and multiplication of mammalian cells on the coating is improved in comparison with the uncoated substrate, or is in any case less adversely affected than the adhesion of bacteria.

From the standpoint of compatibility there are three possible two-way combinations of the groups specified, namely carboxyl and sulfonic acid groups, carboxyl and sulfonate groups, and carboxylate and sulfonate groups, and also two possible three-way combinations, namely carboxyl, carboxylate and sulfonate groups, and carboxyl, sulfo acid and sulfonate groups. All of these combinations constitute advantageous coatings in the sense of the invention. It is of course also possible, as mentioned above, subsequently to convert groups which are present in the coating polymer into functional groups A, for example carboxamide groups (originating, for example, from acrylamide) into carboxyl groups by hydrolysis in an acidic medium. Furthermore, carboxyl groups and sulfonic acid groups can be converted by neutralization (for example in phosphate buffers)into carboxylate and sulfonate groups, respectively. In every case this alters the abovementioned molar ratio of the monomers (a) and (b), possibly with quantitative or even qualitative consequences for the properties of the coating polymer.

An important constituent of the coating polymers is (ii) a copolymerized monomer having a group which is sensitive to UV radiation. As used herein, the term "sensitive to UV radiation" means that the copolymerized monomer contains a functionality which is capable of reacting with the surface to be coated during the grafting reaction, in order to covalently attach the coating polymer to the surface. Suitable such monomers are all those which after copolymerization still have at least one reactive double bond which enables the coating polymer to be grafted onto the activated substrate surface. Examples which may be mentioned are vinylic cinnamoyl or furyl derivatives, and especially cinnamoylethyl acrylate or methacrylate. The monomer which is sensitive to UV radiation is advantageously employed in amounts from 1 to 20 mol-%, advantageously from 3 to 15 mol-%, based on the overall monomers. In the course of free-radically initiated polymerization, the double bond which is [alpha] to the benzene ring is retained as a group sensitive to UV radiation for the subsequent grafting.

The polymers may be prepared in conventional manner by free-radically initiated polymerization, advantageously by solution or emulsion polymerization. Examples of suitable solvents are water; ketones, such as acetone, methyl ethyl ketone and cyclohexanone-ethers, such as diethyl ether, tetrahydrofuran and dioxane; alcohols, such as methanol, ethanol, n- and isopropanol, n- and isobutanol and cyclohexanol, strongly polar solvents, such as dimethylformamide, dimethylacetamide and dimethyl sulfoxide; hydrocarbons, such as

heptane, cyclohexane, benzene and toluene; halogenated hydrocarbons, such as dichloromethane and trichloromethane, esters, such as ethyl acetate, propyl acetate and amyl acetate; and also nitrites, such as acetonitrile.

Examples of suitable polymerization initiators are azo nitrites, alkyl peroxides, acyl peroxides, hydroperoxides, peroxy ketones, peroxy esters and percarbonates, and all customary photoinitiators. The polymerization may be initiated thermally, for example by heating at from 60 to 100 [degrees] C., or by radiation having an appropriate wavelength. After the end of the exothermic polymerization reaction the polymer is separated off from the solvent in a customary manner, for example by precipitation with water, provided the solvent is soluble in water. Monomeric or oligomeric constituents may be removed by extraction with an appropriate solvent.

2. The Substrate Materials

The nature of the substrate to be coated may vary widely. At least a portion of at least one surface of the substrate is coated with the bioactive polymer coating of the present invention. Preferably, the entire surface is coated with the bioactive polymer. Particularly suitable substrate materials are all polymeric substrates, such as polyurethanes, polyamides, polyesters and polyethers, polyether-blockamides, polystyrene, polyvinyl chloride, polycarbonates, polyorganosiloxanes, polyolefins, polysulfones, polyisoprene, polychloroprene, polytetrafluoroethylene (PTFE), polysiloxanes, corresponding copolymers and blends, and also natural and synthetic rubbers, with or without radiation-sensitive groups. The process according to the invention can also be applied to surfaces of painted or otherwise polymer-coated metal, glass or wooden structures. The surfaces of the substrate materials are advantageously freed from adhering oils, greases and other contaminants in a known manner using a solvent before the coating ~~with the coating polymers~~. They may, but need not necessarily, be activated before the coating, as described below. The activation is in some cases carried out in order to achieve better adhesion of the grafted coating to the substrate material. In general, however, the coatings on unactivated substrate surfaces are virtually no different from coatings on activated surfaces with respect to the biological effects and with respect to adhesion.

3. Activation of the Substrate Surfaces

The polymeric substrates may be activated, if desired, by the following methods.

3.1. In the case of the preparation of the substrate polymers it is possible to incorporate, by copolymerization, monomers having groups which are sensitive to UV radiation, in a similar way to that described for the coating polymers. Monomers suitable for this purpose are the same as those which may also be present in the coating polymers. These monomers can be employed, for example, in amounts from 1 to 20 mol-%, advantageously from 3 to 15 mol-%. Polymers modified in this way for sensitivity to radiation can be prepared in a customary manner by means of free-radically initiated polymerization in solution, emulsion or suspension.

3.2. Alternatively, the activation of standard polymers without UV-sensitive groups can be effected by UV radiation, for example in the wavelength range from 100 to 400 nm, preferably from 125 to 310 nm. A suitable source of radiation is, for example, a HERAEUS Noblelight UV excimer device, Hanau, Germany. Mercury vapor lamps, however, are also suitable for substrate activation provided they emit considerable fractions of radiation within the stated ranges. The exposure time is in general from 0.1 second to 20 minutes, preferably from 1 second to 10 minutes, depending on the wavelength and intensity of radiation. It has been found that the presence of oxygen is advantageous. The preferred oxygen pressures are between 2 x 10< - 5> and 2 x 10< - 2> bar. The operation is conducted, for example, in a vacuum of from 10< - 4> to 10< - 1> bar or using an inert gas, such as helium, nitrogen or argon, with an oxygen content of from 0.02 to 20 parts per thousand.

3.3. Activation can also be achieved in accordance with the invention by means of a high-frequency plasma or microwave plasma (Hexagon, Technics Plasma 85551 Kirchheim, Germany) in air or a nitrogen or argon atmosphere. The exposure times are in general from 30 seconds to 30 minutes, preferably from 2 to 10 minutes. The energy employed in the case of laboratory devices is between 100 and 500 W, preferably between 200 and 300 W.

3.4. It is also possible to use corona devices (SOFTAL, Hamburg, Germany) for activation. The exposure times in this case are in general from 1 second to 10 minutes, preferably from 1 to 60 seconds.

3.5. Activation by electron beams or gamma rays (for example from a cobalt 60 source) allows for shorter exposure times which are in general from 1 to 60 seconds.

3.6. Flame treatments of surfaces likewise lead to their activation. Suitable devices, especially those having a barrier flame front, can be constructed in a simple manner or obtained, for example, from ARCOTEC, 71297 Monsheim, Germany. They can be operated with hydrocarbons or hydrogen as combustion gas. In every case, harmful overheating of the substrate must be avoided, which is easily achieved by means of intimate contact with a cooled metal surface on the substrate surface facing away from the side subjected to flame treatment. Activation by flame treatment is restricted, accordingly, to relatively thin, flat substrates, such as sheets. The exposure times amount in general to from 0.1 second to 1 minute, preferably from 0.5 to 2 seconds, the flames involved being-without exception-nonluminous and the distances of the substrate surfaces from the external flame front being from 0.2 to 5 cm, preferably from 0.5 to 2 cm.

3.7. Furthermore, the substrate surfaces can also be activated by treatment with strong acids or strong bases. Suitable strong acids which may be mentioned are sulfuric acid, nitric acid and hydrochloric acid. Polyamides, for example, can be treated at room temperature with concentrated sulfuric acid for from 5 seconds to 1 minute. Particularly suitable strong bases are alkali metal hydroxides in water or in an organic solvent. Thus, for example, dilute sodium hydroxide solution can be allowed to act on the substrate surface at from 20 to 80 [degrees] C. for from 1 to 60 minutes. Alternatively, for example, polyamides can be activated by allowing 2% strength KOH in tetrahydrofuran to act on the surface for from 1 minute to 30 minutes.

3.8. In some cases, for example with highly hydrophobic polymers, it may be advisable to activate the substrate surfaces by a combination of two or more of the methods specified. Very generally, a proven method of substrate activation is that in which the incorporation of UV-sensitive groups (3.1) is combined with UV irradiation (3.2).

4. Coating by Graft Polymerization

After one of the activating pretreatments described under 3.2 to 3.8, the substrates with the activated surfaces may be exposed for from 1 to 20 minutes, preferably from 1 to 5 minutes, to the action of oxygen, for example in the form of air. Alternatively, a solvent, such as tetrahydrofuran, can be allowed to act on the activated surfaces for a similar length of time. Subsequently, the surfaces that have been activated (including those which have if desired been activated in accordance with 3.1), but also those which have not been activated, are coated by known methods, such as dipping, spraying or brushing, with a solution of the coating polymer which is to be used in accordance with the invention. Solvents which have been found suitable are, for example, ethers, such as tetrahydrofuran, and/or strongly polar solvents, such as dimethyl sulfoxide, although other solvents can also be used provided they have sufficient solvency for the monomers and provide good wetting of the substrate surfaces. Depending on the solubility of the polymers and on the desired film thickness of the grafted coating, the concentrations of the polymer in the solution can be in general from 0.1 to 50 percent by weight. Solutions with a content of coating polymer of from 3 to 15% by

weight, advantageously of about 10% by weight, have been found appropriate in practice and give rise in general and in one pass to coherent coatings which cover the substrate surface and have film thicknesses which can be more than 0.1 [mu] m.

Following or even during the evaporation of the solvent, the grafting of the applied coating polymer is brought about, judiciously by radiation in the short wave segment of the visible region or in the long wave segment of the UV region of electromagnetic radiation, to form covalent bonds to the substrate surface. Highly suitable radiation, for example, is that of a UV excimer of the wavelengths 250 to 500 nm, preferably from 290 to 320 nm. Here again, mercury vapor lamps have been found suitable provided they emit considerable fractions of radiation within the stated ranges. The exposure times are in general from 10 seconds to 30 minutes, preferably from 2 to 15 minutes.

In some cases it is judicious to repeat the above-described operations, optionally including the activation, in order by means of such a multicoat technique to ensure a hermetically sealed and/or relatively thick coating. Alternatively, it is also possible to immerse the optionally surface-activated substrate, if desired after the oxygen or solvent treatment described above, into the solution of the coating polymer which is to be used in accordance with the invention and to irradiate it in the immersed state. By means of simple experiments it is not difficult to ascertain the irradiation times with a given radiation source and the substrate/solution contact times, which may be relatively long, required to achieve the desired film thickness.

The process according to the invention for the anti-bacterial modification of the surface of substrates, and especially polymer substrates, permits the precise establishment of molar ratios of different functional groups which are optimal for inhibiting bacterial adhesion and/or propagation and for regulating cell proliferation behavior. It is a particular advantage of the process and of the coated substrates according to the invention that the latter, moreover, show good blood compatibility. Furthermore, the process offers the advantage that plastics which have already become established can, while retaining their mechanical properties and their form, be additionally modified so as to be anti-bacterial and, alternatively, to inhibit or to promote cell proliferation. No further treatments before or after are necessary as long as problem-free wetting and chemical bonding to the substrate surfaces are possible. Highly hydrophobic plastics may require a hydrophilicizing pretreatment, for example by chemical etching with acids or bases or by plasma treatment, in order to attain sufficient wettability by the solution of the coating polymer. In this case the highly hydrophobic plastics are hydrophilicized at the same time and surface-activated in the sense of the present invention.

Articles which have been coated in accordance with the processes of the present invention and thereby modified to make them antibacterial are suitable as biocompatible materials for use in the biotechnical and/or medical fields, for example for storage or packaging purposes or for hoses or pipelines. Examples of medical articles are catheters, hoses, wound drainage devices, dressings, **stents,** intraocular lenses, pacemakers and cardiac valves.

The substrates an articles may also used as implants in patients in need thereof. The substrates/articles of the present invention may be implanted into a patient in need thereof according to the well-known procedures routinely used in the field of biomedical implants. As used herein, the terms "implant" and "implanted" include articles and substrates that are applied to the skin surface of a patient, e.g., a wound dressing, as well to articles which are implanted into the body, e.g., pacemakers and cardiac valves. In these applications, the substrate and article implants are contacted with the biological fluid of the patient.

Having generally described this invention, a further understanding can be obtained by reference to certain specific examples which are provided herein for purposes of illustration only and are not intended to be limiting unless otherwise specified.

EXAMPLES

The coating polymers used in the examples are representative of a large number of other polymers having monomers which fall under the formulae I to IV.

(1) Investigations of Bacterial Adhesion

Measurement of the Bacterial Adhesion on Films of Coating Polymers by Scintillation

These films were prepared in order to compare their antibacterial properties with those of antibacterially coated substrate films according to the invention.

Samples of the coating polymers (Examples 1 to 9 below) obtained by copolymerization are dissolved in an appropriate solvent, such as chloroform. The solutions are poured into a Petri dish and the solvent is evaporated, and then the resulting polymer films are immersed for a period of one hour in 1 ml of a solution consisting of 0.4 g/l bovine serum albumin (BSA), dissolved in phosphate-buffered physiological saline solution (PBS), and 20 [mu] g/ml purified human fibronectin. The samples thus coated with fibronectin are then placed with vigorous stirring for 1 hour at 37 [degrees] C. in a suspension of the respective bacteria, which have been radiolabeled by incorporation of <3>H-thymidine. After the predetermined period has elapsed the excess bacteria are removed by washing, and the polymer films are rinsed twice with 3 ml each time of a PBS-BSA solution, and, in order to determine the number of adhering bacteria, are placed in a glass vessel with a screw closure containing 20 ml of scintillation solution. The percentage of adhering bacteria is determined by way of the ratio of the radioactivity present in the sample to the radioactivity introduced originally by the bacteria. The inhibition of bacterial adhesion is expressed as a percentage relative to the bacterial adhesion of an untreated film as an external standard.

Measuring the Bacterial Adhesion of Coated Standard Films by ATP Determination (Static)

Following adsorption of the bacterial cells on immersed polymer films, the nonadhering bacteria are rinsed off with sterile PBS buffer solution. Adenosine triphosphate (ATP), a substance present in the cells, is extracted from the adhering bacteria in a customary manner and is determined using a customary commercial test combination in a bioluminometric assay. The number of light pulses measured is proportional to the number of adhering bacteria. In each case, a number of film sections are employed. The value measured with the uncoated, standard film is taken as being equal to one hundred percent, and the bacterial adhesion values of the antibacterially coated films are expressed as a percentage reduction.

Measuring the Bacterial Adhesion of Coated Standard Films by ATP Determination (Dynamic)

The bacteria are placed together with the section of film to be tested in a yeast extract/peptone/glucose nutrient solution and are shaken at 37 [degrees] C. for 24 hours. Following this, the section of film is rinsed with tapwater, transferred to a fresh flask containing nutrient solution, and shaken at 37 [degrees] C. for a further 24 hours. This cycle is repeated once more, and the film section is rinsed with tapwater. The adenosine triphosphate (ATP), a substance present in cells, is extracted from the bacteria which are adhering to the film and is determined using a customary commercial test combination in a bioluminometric assay. Since the boundary conditions applying to the dynamic measurement are the same as those for the static measurement, the bacterial adhesion values of the coated films are expressed as a percentage reduction in comparison with uncoated, standard films.

(2) Investigations of Cell Proliferation

Conditioning the Polymer Films (Substrate Films)

The films coated in accordance with the invention, and uncoated comparison films, are

washed twelve times for 3 hours each time at 37 [degrees] C. in ethanol. The films pretreated in this way are subsequently washed three times for 3 hours in each case in a 0.15-molar sodium chloride solution and then rinsed off with water. In the following purification step, the films are placed three times for 3 hours in each case into a phosphate buffer solution and then irradiated with UV light for 15 minutes. The films thus pretreated are stored for 16 hours at 37 [degrees] C. in a DMEM (Dulbecco's Modified Eagles Medium) solution. Finally, the films are kept for 16 hours at 37 [degrees] C. in a DMEM solution to which 0.05% antibiotics, 200 mg/l L-glutamine and 10% fetal calf serum are added, under an atmosphere of 5% CO<2> and 95% air.

Preparing the Cell Suspension

Human fibroblasts (McCoy's) from ATCC No. CRL 1996 (Rockville, Md., USA) are grown in a DMEM medium containing 0.05% antibiotics, 200 mg/l L-glutamine and 10% fetal calf serum at 37 [degrees] C. under an atmosphere of 5% CO<2> and 95% air. After isolating the cells from the nutrient medium, both the number of living cells and the total number of cells are determined in a customary manner.

Measuring the Cell Proliferation Properties

The films coated in accordance with the invention and the comparison films, following the pretreatment described above, are then placed in wells in standard microliter plates and held by means of special PTFE inserts which have been sterilized beforehand with ethanol. Films, wells and PTFE inserts are sterilized by irradiation with UV light for 16 minutes. Subsequently, the cell suspension is added to the polymer films. After incubation for 8 days at 37 [degrees] C. the cells are purified by means of phosphate buffer solution, separated off with 0.05% by weight trypsin-EDTA solution, and counted optically or using a cell counter.

(3) Preparation of the Coating Polymers

Example 1

A monomer mixture comprising 5 mol %-tris(trimethylsiloxy)methacryloyloxypropylsilane (TTMPS), 10 mol % cinnamoylethyl methacrylate (CEM), 13.7 mol % methacrylic acid (MA) and 11.3 mol % dimethyloctylammonium styrenesulfonate (DOASS) is introduced into a reaction vessel in THF as solvent under inert gas, and this initial charge is heated to 65 [degrees] C. On reaching this temperature, 0.6 mol % of azobisisobutyronitrile is added. After a reaction period of 24 hours, the quaterpolymer is isolated by removing the solvent on a rotary evaporator and then is washed with water. NMR analysis of the product reveals a composition of

TTMPS	CEM	MA	DOASS	
72	8.2	10.8	9	mol %

The ratio of COOH or COO< -> to SO<3>< -> is 1.2.

Example 2

A monomer mixture comprising 75 mol % tris(trimethyl-siloxy)methacryloyloxypropylsilane (TTMPS), 10 mol % cinnamoylethyl methacrylate (CEM), 10 mol % methacrylic acid (MA) and 5 mol % dimethyloctylammonium styrene-sulfonate (DOASS) is introduced into a reaction vessel in THF as solvent under inert gas, and this initial charge is heated to 65 [degrees] C. On reaching this temperature, 0.6 mol % of azobisisobutyronitrile is added. After a reaction

period of 24 hours, the quaterpolymer is isolated by removing the solvent on a rotary evaporator and then washed with water. NMR analysis of the product reveals a composition of

TTMPS	CEM	MA	DOASS	
84	9.6	2.1	3.8	mol %

The ratio of COOH or COO< -> to SO<3>< -> is 0.55.

Example 3

55 mol % of methyl methacrylate, 35 mol % of methacrylic acid, 5 mol % of sodium styrenesulfonate and 5 mol % of cinnamoylethyl methacrylate are dissolved in dimethyl sulfoxide under inert gas. After reaching the reaction temperature of 70 [degrees] C., 0.6 mol % of azobisisobutyronitrile, dissolved in dimethyl sulfoxide, is added dropwise. After a reaction period of 18 hours the product is precipitated with ice-water and subsequently subjected to extraction with acetone and water in a Soxhlet. Drying is conducted at 50 [degrees] C. in vacuo.

Example 4

65 mol % of methyl methacrylate, 18 mol % of methacrylic acid, 12 mol % of sodium styrenesulfonate and 5 mol % of cinnamoylethyl methacrylate are dissolved in dimethyl sulfoxide under inert gas. After reaching the reaction temperature of 75 [degrees] C., 0.6 mol % of azobisisobutyronitrile, dissolved in dimethyl sulfoxide, is added dropwise. After a reaction period of 16 hours the product is precipitated with ice-water and subsequently subjected to extraction with acetone and water in a Soxhlet. Drying is conducted at 50 [degrees] C. in vacuo.

Example 5

80 mol % of methyl methacrylate, 10 mol % of acrylic acid, 5 mol % of sodium styrenesulfonate and 5 mol % of cinnamoylethyl methacrylate are initially introduced in dimethyl sulfoxide under inert gas. After reaching the reaction temperature of 75 [degrees] C., 0.6 mol % of azobisisobutyronitrile, dissolved in dimethyl sulfoxide, is added dropwise. After a reaction period of 16 hours the product is precipitated with ice-water and subsequently subjected to extraction with acetone and water in a Soxhlet. Drying is conducted at 50 [degrees] C. in vacuo.

Example 6

87.5 mol % of methyl methacrylate, 5 mol % of maleic anhydride, 2.5 mol % of sodium styrenesulfonate and 5 mol % of cinnamoylethyl methacrylate are initially introduced in dimethyl sulfoxide under inert gas. After reaching the reaction temperature of 70 [degrees] C., 0.6 mol % of azobisisobutyronitrile, dissolved in dimethyl sulfoxide, is added dropwise. After a reaction period of 16 hours the product is precipitated with ice-water and subsequently subjected to extraction with acetone and water in a Soxhlet. Drying is conducted at 50 [degrees] C. in vacuo.

Example 7

80 mol % of methyl methacrylate, 8 mol % of methacrylic acid, 7 mol % of sodium styrenesulfonate and 5 mol % of cinnamoylethyl methacrylate are initially introduced in dimethyl sulfoxide under inert gas. After reaching the reaction temperature of 70 [degrees]

C., 0.6 mol % of azobisisobutyronitrile, dissolved in dimethyl sulfoxide, is added dropwise. After a reaction period of 16 hours the product is precipitated with ice-water and subsequently subjected to extraction with acetone and water in a Soxhlet. Drying is conducted at 50 [degrees] C. in vacuo.

Example 8

85 mol % of methyl methacrylate, 7.5 mol % of maleic anhydride, 2.5 mol % of sodium styrenesulfonate and 5 mol % of cinnamoylethyl methacrylate are initially introduced in dimethyl sulfoxide under inert gas. After reaching the reaction temperature of 70 [degrees] C., 0.6 mol % of azobisisobutyronitrile, dissolved in dimethyl sulfoxide, is added dropwise. After a reaction period of 18 hours the product is precipitated with ice-water and subsequently subjected to extraction with acetone and water in a Soxhlet. Drying is conducted at 50 [degrees] C. in vacuo.

Example 9

65 mol % of methyl methacrylate, 18 mol % of methacrylic acid, 12 mol % of triethylammonium styrenesulfonate and 5 mol % of cinnamoylethyl methacrylate are initially introduced in dimethyl sulfoxide under inert gas. After reaching the reaction temperature of 70 [degrees] C., 0.6 mol % of azobisisobutyronitrile, dissolved in dimethyl sulfoxide, is added dropwise. After a reaction period of 16 hours the product is precipitated with ice-water and subsequently subjected to extraction with acetone and water in a Soxhlet. Drying is conducted at 50 [degrees] C. in vacuo.

The radiation-sensitive monomer used, cinnamoylethyl methacrylate, is obtained starting from 2-hydroxyethyl methacrylate (3.8 mmol) and cinnamoyl chloride (3.8 mmol) in 100 ml of dry ethyl ether at room temperature in the presence of 3.8 mmol of pyridine.

Example 10

A monomer mixture comprising 59 mol % of tris(trimethylsiloxy)methacryloyloxypropylsilane (TTMPS), 16 mol % of cinnamoylethyl methacrylate (CEM), 13.7 mol % of methacrylic acid (MA) and 11.3 mol % of dimethyloctylammonium styrenesulfonate (DOASS) in THF as solvent is heated to 65 [degrees] C. under nitrogen as protective gas. When this temperature is reached, 0.6 mol % of azobisisobutyronitrile (AIBN) in THF is metered in as solvent over a period of 1 hour. After a reaction time of 24 hours, the quaterpolymer is isolated by removing the solvent in a rotary evaporator and then washed with water. NMR analysis of the product provides a composition of

TTMPS	CEM	MA	DOASS	
66.7	13.1	11.6	8.6	mol %

The ratio of COOH or COO< -> to SO<3>< -> is 1.4.

Example 11

A monomer mixture comprising 60.4 mol % of tris(trimethylsiloxy) methacryloyloxypropylsilane (TTMPS), 18 mol % of cinnamoylethyl methacrylate (CEM), 9.5 mol % of methacrylic acid (MA) and 12.1 mol % of dimethyloctylammonium styrenesulfonate (DOASS) in THF as solvent is heated to 65 [degrees] C. under nitrogen as protective gas. When this temperature is reached, 0.6 mol % of azobisisobutyronitrile (AIBM) in THF is metered in as solvent over a period of 1 hour. After a reaction time of 24 hours, the

quaterpolymer is isolated by removing the solvent in a rotary evaporator and is then washed with water. NMR analysis of the product provides a composition of

TTMPS	CEM	MA	DOASS	
68.5	13.8	7.6	10.1	mol %

The ratio of COOH/COO< -> to SO<3>< -> is 0.8.

(4) Grafting the Coating Polymers onto Substrate Films

The grafting is carried out using the cinnamoyl-containing grafting polymers prepared above. The substrates were coated by photografting. The coating polymers of Examples 1 to 9 were grafted onto activated polymeric substrates and the coating polymers of Examples 10 and 11 onto unactivated polymeric substrates.

The grafting of the coating polymers onto activated surfaces was carried out as follows:

The activation is carried out by UV irradiation using a Hg vapor lamp (100 M, and the grafting is initiated by irradiation with the same lamp.

The various substrate films are irradiated for 20 minutes and then immersed in THF for 15 minutes.

A solution of the coating polymer (10 g/l) in THF-dimethyl sulfoxide (80/20) is sprayed onto 2 samples of the substrate film.

The two samples are irradiated for 10 minutes.

The grafting onto unactivated surfaces was carried out as follows:

2 samples of a silicone (polysiloxane) substrate film are sprayed with a solution of the quaterpolymer (10 g/l) in THF/dimethyl sulfoxide (80:20).

The samples are irradiated for 10 minutes using a 100 W mercury vapor lamp (distance between sample and lamp 2 cm).

The grafting is demonstrated by the substrate having an increase in weight of 15.9% (Example 10) and 18.3% (Example 11) after extraction with water (6 h at 60 [degrees] C.). Crosslinking and grafting occur by means of the double bonds in the [alpha] position: ◆ Get Chemical Structure

Photocrosslinking by means of the radiation-sensitive groups can be observed using IR spectroscopy. Whereas the IR spectrum of the substrate already coated with the coating polymer but not yet subjected to UV irradiation has a band at 1637 cm< - 1>, which is assigned to the C = C double bonds, following UV irradiation this band can no longer be detected.

(5) Results of the Test for Bioactive Properties

The results of the test for bioactive properties of the coated substrate films are evident from FIGS. 1-7. FIGS. 1 to 6 demonstrate the antibacterial properties of the coating polymers according to the invention. The scintillation values are obtained with films of the coating polymers. It is seen that the antibacterial properties of the substrate films coated in

accordance with the invention are very similar to those of the films of the coating polymers.

From FIG. 7 it is evident that in the range of the proportion of CO<2>< -> /SO<3>< -> up to about 3 there is a marked reduction in the cell growth, whereas around the range between about 2 and about 5 the cell proliferation corresponds approximately to that of the uncoated film and are in any case considerably less reduced than the bacterial adhesion in the same range.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

CLAIMS:

What is claimed as new and desired to be secured by Letters Patent of the United States is:

[*1] 1. A process for preparing a bioactive, covalently fixed coating on the surface of a substrate, the process comprising:preparing a coating polymer which comprises, in copolymerized form, (i) at least one monomer represented by the formula (I):

R-(A)<a> (I), where R is a mono- or diolefinically unsaturated organic radical having a valence a; each A is, independently, a carboxylic acid group, sulfuric acid group, sulfonic acid group, phosphoric acid group, phosphonic acid group, phosphorous acid group, a phenolic hydroxyl group, or a salt of one of said acid groups; and a is 1, 2 or 3; and (ii) at least one monomer which in copolymerized form is sensitive to ultraviolet radiation; and then grafting the coating polymer to at least a portion of a surface of a substrate under UV radiative induction, wherein (i) comprises (a) a monomer having carboxylic acid and/or carboxylate groups and (b) a monomer having sulfonic acid and/or sulfonate groups, and the molar proportion of (a) + (b) in the coating polymer is 5 to 40%.

[*2] 2. The process of claim 1, wherein (i) comprises at least one monomer represented by formula (II) or (III):

(C<n>H<2n - q - x>)(COOR<1>)<x> (II)

(C<n>H<2n - q - x>)(SO<3>R<1>)<x> (III)

whereineach n is, independently, an integer from 2 to 6; each x is, independently, 1 or 2; each q is, independently, 0 or 2, and each R<1> is, independently,-H or an equivalent of a metal ion.

[*3] 3. The process of claim 1, wherein (i) comprises at least one benzene-derived monomer represented by formula IV:

(C<6>H<m>)B<b>R<3><c>(OH)<d> (IV),

whereinm is 6 - b - c - d; and each B is, independently, a mono- or diolefinically unsaturated straight-chain or branched radical of the formula

-(C<n>H<k>)(COOR<1>)<x>

or

-(C<n>H<k>)(SO<3>R<1>)<x>,

whereink is 2n - 1 - g - x; each n is, independently, an integer from 2 to 6; each x is,

independently, 1 or 2; each q is, independently, 0 or 2; each R<1> is, independently,-H or an equivalent of a metal ion; each R<3> is, independently, C<1-4>-alkyl,-NH<2>,-COOH,-SO<3>H,-OSO<3>H,-OPO(OH)<2>,-PO(OH)<2>,-OP(OH)<2>,-OPO(O< ->) OCH<2>CH<2>N< +> (CH<3>)<3>,-PO(O< ->)OCH<2>CH<2>N< +> (CH<3>)<3>,-OP (O< ->)O-CH<2>CH<2>N< +> (CH<3>)<3>, or a salt thereof; b is 1, 2 or 3; c is 0, 1, 2 or 3; and d is 0, 1, 2 or 3, with the proviso that b + c + d is [less than or equal to] 6.

[*4] 4. The process of claim 1, wherein (i) comprises a monomer having a carboxyl group, a is 2 or 3 or a carboxylate group, and the monomer having a carboxyl group or a carboxylate group includes at least one other radical A which is not a carboxyl group or a carboxylate group; orwherein (i) further comprises a second monomer which has a radical A which is not a carboxyl group or a carboxylate group.

[*5] 5. The process of claim 1, wherein (a) and (b) are present in a molar ratio, wherein the molar ratio of (a) to (b) is < 10.

[*6] 6. The process of claim 1, wherein (a) and (b) are present in a molar ratio, wherein the molar ratio of (a) to (b) is from 0.5 to 10.

[*7] 7. The process of claim 1, wherein (a) and (b) are present in a molar ratio, wherein the molar ratio (a) to (b) is from 0.4 to 3, and the coating polymer is antibacterial and inhibits cell proliferation.

[*8] 8. The process of claim 1, wherein monomer (a) and monomer (b) are present in a molar ratio, wherein the molar ratio of the monomer (a) to the monomer (b) is from 2 to 5, and the coating polymer is antibacterial and promotes cell proliferation.

[*9] 9. The process of claim 1, wherein the monomer (ii) is a cinnamoyl derivative or furyl derivative.

[*10] 10. The process of claim 9, wherein (ii) comprises a cinnamoylethyl acrylate or methacrylate.

[*11] 11. The process of claim 1, wherein the surface of the substrate contains a copolymerized monomer having a group which is sensitive to UV radiation.

[*12] 12. The process of claim 1, wherein the substrate surface is activated by ultraviolet radiation prior to the grafting step.

[*13] 13. The process of claim 1, wherein the grafting is induced by ultraviolet radiation.

[*14] 14. A process according to claim 1, wherein monomer (i) comprises acrylic acid and monomer (ii) comprises cinnamoylethyl methacrylate.

[*15] 15. A process according to claim 1, wherein the coating polymer is antibacterial and either inhibits or promotes cell proliferation.

[*16] 16. A process for preparing a covalently fixed coating on the surface of a substrate, comprising:(a) preparing a coating polymer which comprises, in copolymerized form, (i) at least one monomer represented by the formula (I):

R-(A)<a> (I), wherein R is a mono- or diolefinically unsaturated organic radical having a valence a; each A is, independently, a carboxylic acid group, sulfuric acid group, sulfonic acid group, phosphoric acid group, phosphonic acid group, phosphorous acid group, a phenolic hydroxyl group, or a salt of one of said acid groups; and a is 1, 2 or 3; and (ii) at least one monomer which is sensitive to ultraviolet radiation; and then (b) dissolving the coating polymer in a solvent; (c) transferring the coating polymer in the solvent to the surface of the

substrate; and (d) grafting the coating polymer to at least a portion of a surface of the substrate under ultraviolet radiative induction.

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*Pat. No. 6090901, **

6,090,901

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Jul. 18, 2000

Polymeric **surface coatings**

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Continuation-in-part of Application No. 8-475,620, Jun. 7, 1995 now patented 5,705,583
Which is a continuation-in-part of Application No. 8-175,348, Mar. 7, 1994 now patented 5,648,442

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CL: 526

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CORE TERMS: polymer, monomer, comonomer, alkyl, formula, hydrogen, atom, bond, coated, valence, methacrylate, coating, reactive, carbon, binding, sample, zwitterionic, methyl, mole, nitrogen, alkylene, optionally, residue, diluent, mixture, ethyl, acid, solvent, minute, phosphate

ABST:
A non-crosslinked polymer having pendant zwitterionic groups and pendant functional groups can be coated from a coating composition onto a surface having pendant coreactive functional groups and, after coating, may be cured so that covalent bonds are formed between the coreactive functional groups on the polymer and the surface. Alternatively the polymer can be crosslinked after coating, by formation of covalent intermolecular cross-links between coreactive pendant functional groups on the polymer. The zwitterionic pendant groups preferably have, as the anion, a phosphate ester group, and as the cation, a quaternary ammonium group. The polymer coating is stable and provides improved biocompatibility, especially haemocompatibility.

NO-OF-CLAIMS: 15

EXMPL-CLAIM: 1

NO-OF-FIGURES: 2

NO-DRWNG-PP: 1

PARCASE: This is a Continuation-in-Part of application Ser. No. 08/475,620 filed on Jun. 7, 1995, now U.S. Pat. No. 5,705,582 which was a continuation-in-part of Ser. No. 08/175,348 filed Mar. 7, 1994 (now U.S. Pat. No. 5,648,442).

SUM:

BACKGROUND OF THE INVENTION

The present invention relates to new polymers, processes for producing them and processes for coating surfaces with them. The invention also provides improved processes for producing certain monomers and to certain new monomers used to obtain the polymers. The polymers are useful for coating surfaces of devices and materials which come into contact with protein-containing solutions and biological fluids, and rendering the surfaces bio- and haemocomaptible. Surfaces may thus be rendered suitable for prolonged contact with living tissues and body fluids and with protein-containing solutions.

RELEVANT PRIOR ART

Materials used in the manufacture of separation substrates and devices, blood contacting devices contact and intraocular lenses, and other devices which are used in contact with protein-containing or biological fluids must be selected on the basis of acceptable physical and mechanical properties and compatability with the protein-containing or biological fluid. For any given application of these materials it is usually difficult to optimise all of these considerations simultaneously and a compromise must be reached often resulting in less than optimal performance. For example, major biological problems are often encountered with materials which have otherwise optimal mechanical and physical properties. These problems often manifest themselves as undesirable deposition of biological components and in particular proteinaceous material. This protein adsorption results in blood clot formation in blood-contacting materials, the adsorption of tear components onto contact lenses resulting in deposit formation, formation of deposits on intraocular lenses and in separation media it results in blockage and failure of separation devices. Such effects lead to significant loss in operational performance and often complete rejection and failure of devices.

In the case of medical devices, for example prostheses and components of blood dialysis equipment, it is common practice to employ biocompatible polymers to form at least the surface of the devices to discourage protein adsorption. However, these materials are not perfect and reaction with the living tissues still remains a problem; for example surface-induced thrombosis is still a major difficulty, particularly where large quantities of blood are contacted with a foreign surface such as in artificial lungs and kidneys. Formation of a clot in an artificial organ has a number of adverse or even catastrophic effects including occlusion of the blood pathway in the extracorporeal system, or embolism if the clot breaks off the artificial surface and lodges in a host blood vessel. Dialysis membranes, heart valves, circulator-assist devices, blood substitutes and artificial lungs all share this problem.

It is known that materials for use as biocompatible coatings should ideally:

(a) be capable of reproducible manufacture as pure materials;

(b) be capable of being coated onto surfaces without being degraded or adversely changed;

(c) have the requisite mechanical and permeability properties required for the specific function of the device for which they are intended;

(d) be sterilisable without adverse changes in, for example, permeability and mechanical or surface properties;

(e) not be damaged or degraded by the biological environment;

(f) not be carcinogenic.

In applications involving direct contact with blood further restrictions exist. Materials should not:

(g) induce significant platelet adhesion;

(h) interfere with the normal clotting mechanism; or

(i) cause any significant damage to the cellular elements or soluble components of the blood.

There have been many attempts to prepare biocompatible, and specifically blood compatible (i.e. haemocompatible), surfaces, which do not activate the blood coagulation process and do not promote thrombus formation. Examples of such attempts include the preparation of negatively charged surfaces, such as by use of anionic polymers or suitable oriented electret polymers, preparation of surfaces coated with the natural anticoagulant heparin or synthetic heparin analogues, preparation of surfaces with inherently low surface free energy such as by use of silicone rubber, preparation of albumin-coated surfaces, and preparation of surfaces coated with compounds such as some polymethanes which are thought to adsorb albumin preferentially from blood. All of these however have had limitations.

We have now devised new film-forming polymers which can be used to coat surfaces. It has been found that these copolymers may be used to provide stable coatings on a wide variety of surfaces including, polyethylene, PVC, steel and poly(imide). The invention also provides physiadsorbable polymers which when used to coat surfaces, do not swell, to any significant extent, in aqueous environments; in some situations swelling in aqueous environments can reduce the stability of coatings of physiadsorbable polymers on surfaces.

The polymers which contain zwitterionic groups, mimic the zwitterionic structure of phospholipids such as phosphatidylcholine and sphingomyelin which are the major components of the outer membrane of all living cells. In this way the present invention seeks to provide a biocompatible surface on a coated substrate at which the deposition of proteins and cells at the substrate is minimised when the coated substrate comes into contact with a protein-containing solution or biological fluid.

In addition a variety of ligands may be attached to the polymers of the present invention when coated onto a substrate. Alternatively ligands may be attached to the polymers prior to coating on a substrate, e.g. when the polymer is in solution. The polymers of the present invention may therefore provide a means of attachment of such ligands. The term ligand includes, but is not limited to, specific binding agents such as immunoglobulins and associated fragments thereof such as those useful for affinity separation and diagnostic applications, photosensitive and chemisensitive moieties such as those useful for detector and sensor applications and therapeutic agents useful for clinical applications. Other ligands include peptide fragments which may be chemically linked to a polymer of the invention, such as fragments which induce cell attachment and may therefore be used to allow the polymers of the present invention to provide cell seeding.

SUMMARY OF THE INVENTION

The present invention provides a polymer of one or more radical polymerisable, preferably ethylenically unsaturated, monomers, which polymer has pendant zwitterionic groups bearing a centre of permanent positive charge and other pendant groups capable of stably binding the polymer to a surface. Such coatings bind to surfaces with good adhesion and are not removable in the environment in which the coated surfaces are used, e.g. in use as a coating on a blood-contacting surface.

Zwitterionic groups mimic the structure of the head groups of phospholipids in cells. Without wishing to be limited by this theory, it is thought that the presence of such groups at a surface renders the surface more biocompatible.

The extent to which a polymer renders a surface biocompatible may be assessed as a combination of factors such as reduction in the extent to which the surface causes blood platelet activation, protein adsorption, (for instance as judged by absorption of fibrinogen from human plasma) and reaction with C-reactive protein which is caused by the presence on the surface of isolated zwitterionic, e.g.) phosphate ammonium ester groups. Preferably the polymers of the invention when coated onto a substrate, provide a reduction in platelet activation of at least 70%, more preferably at least 90%, as assessed by the assay described hereinafter compared to an untreated substrate. It is also preferred that the polymers of the invention, when coated onto a substrate, provide a reduction in fibrinogen absorption of at least 60% as assessed by the assay described hereinafter and a protein index of less than 1.5 x 10 compared to an untreated substrate. The protein index is defined as the ratio of the absorbance due to C-reative protein measured in the assay described hereinafter to the reduction in fibrinogen adsorption.

The nature of the groups capable of binding the polymer to a surface will be selected depending upon the nature of the surface which it is intended to coat with the polymer. Where the surface is hydrophobic, groups capable of being physisorbed at the surface may be used to bind the polymer to the surface. Where the surface is hydrophillic and bears functional groups then groups which are capable of reacting with surface functional groups to form covalent bonds may be used to bind the polymer to the surface. Where the surface is charged then groups bearing ionic charge may be used to bind the polymer to the surface by ionic interactions.

Polymers of the invention may therefore bind to a surface by physisorption, covalent or ionic bonding depending upon the precise nature of the surface. In certain cases it may be possible to use two of these binding mechanisms in combination.

In the present invention the polymer must include reactive groups capable of forming covalent bonds with a substrate surface of with coreactive groups on the polymer to cross-link it at the surface after coating. For polymers which cross-link initial surface binding may be provided by hydrophobic or ionic bonding.

It will be understood that throughout, where a group is referred to as capable of binding a polymer to a surface this is intended to mean stably binding.

Where a hydrophobic surface is to be coated, alkyl groups of 6 or more carbon atoms, or fluoroalkyl groups, optionally having one or more etheric oxygen atoms interrupting the carbon chain, and optionally containing one or more carbon-carbon double or triple bonds, or siloxane groups, preferably containing from 1 to 50, more preferably 5 to 30, silicon atoms, may be used as the pendant groups capable of binding the polymer to a surface. Such groups are capable of forming strong secondary valence interactions with a surface, and being physisorbed at a hydrophobic surface, i.e. adsorbed without formation of a covalent interaction.

Thus according to the invention there is provided a polymber obtainable by copolymerising a radical polymerisable, preferably ethylenically unsaturated, zwitterionic comonomer and a radical polymerisable, preferably ethylenically unsaturated, comonomer bearing a reactive group.

Such a polymer may be a copolymer comprising residues of a radical polymerisable, preferably ethylenically unsaturated, comonomer containing a zwitterionic group, which bears a centre of permanent positive charge, and a radical polymerisable, preferably ethylenically unsaturated, comonomer bearing a reactive group is capable of covalently binding to a surface, and/or of crosslinking the polymer.

In the present specification the terms reactive and functional in definitions of pendant groups of monomers, polymers or substrate surfaces are intended to have the same meaning unless

apparent from the context.

DETAILED DESCRIPTION OF THE INVENTION

The invention is directed to a substantially non-cross-linked polymer formed by radical polymerisation of radical polymerisable monomers including

i) a zwitterionic monomer having the formula:

Y-B-X(I)

wherein

B is a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene chain optionally containing one or more fluorine atoms up to and including perfluorinated chains, or if X contains a carbon-carbon chain between B and the centre of permanent position charge or if Y contains a terminal carbon atom bonded to B, a valence bond;

X is a zwitterionic group selected from groups IVB, IVC, IVD and IVF in which group IVB has the formula [See Original Patent for Chemical Structure Diagram]

wherein

the groups R<6 > are the same or different and each is hydrogen or C[1-4]alkyl and d is from 2 to 4;

group IVC has the formula [See Original Patent for Chemical Structure Diagram]

where

the groups R<7 > are the same or different and each is hydrogen or C[1-4]alkyl, and e is from 1 to 4;

group IVD has the formula [See Original Patent for Chemical Structure Diagram]

wherein

the groups R<8 > are the same or different and each is hydrogen or C[1-4]alkyl, R<8a > is hydrogen or a group -C(O)B<1> R<8b > wherein R<8b > is hydrogen or methyl, B<1 > is a valence bond or straight or branched alkylene, oxaalkylene or oligo-oxaalkyene group, and f is from 1 to 4; and if B is other than a valence bond z is 1 and if B is a valence bond z is 0, if X is directly bonded to an oxygen or nitrogen atom and otherwise z is 1;

group IVE has the formula [See Original Patent for Chemical Structure Diagram]

wherein

the groups R<9 > are the same or different and each is hydrogen or C1-C4 alkyl, R<9a > is hydrogen or a group -C(O)B<2> R<9b> , wherein R<9b > is hydrogen or methyl, B<2 > is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group, and g is from 1 to 4; and

if B is other than a valence bond z is 1 and if B is a valence bond z is 0 if X is directly bonded to an oxygen or nitrogen atom and otherwise z is 1; and

group IVF has the formula [See Original Patent for Chemical Structure Diagram]

wherein

the groups R<10 > are the same or different and each is hydrogen or C[1-4]alkyl, R<10a > is hydrogen or a group -C(O)B<3> R<10b > wherein R<10a > is hydrogen or methyl, B<3 > is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group, and h is from 1 to 4; and

if B is other than a valence bond z is 1 and if B is a valence bond z is 0 if X is directly bonded to the oxygen or nitrogen and otherwise z is 1 and

Y is an ethylenically unsaturated polymerisable group selected from [See Original Patent for Chemical Structure Diagram]

wherein:

R is hydrogen or a C1-C4 alkyl group;

A is -O- or -NR<1> - where R<1 > is hydrogen or a C1-C4 alkyl group or R<1 > is -B-X where B and X are as defined above; and

K is a group -(CH2)[p]OC(O)-, -(CH2)[p]C(O)O-, -(CH2)[p]OC(O)O-, -(CH2)[p]NR<2> -, (CH2)[p]NR<2> C(O)-, -(CH2)[p]C(O)NR<2> -, -(CH2)[p]NR<2> C(O)O-, -(CH2)[p]OC(O) NR<2> -, -(CH2)[p]NR<2> C(O)NR<2> -, (in which the groups R<2 > are the same or different) -(CH2)[p]O-, -(CH2)[p]SO3-, or, optionally in combination with B, a valence bond and p is from 1 to 12 and R<2 > is hydrogen or a C1-C4 alkyl group and

ii) a monomer having a reactive group of the formula general formula (XII)

Y<2> -B<7> -Q<3(XII)>

where

Y<2 > is an ethylenically unsaturated polymerisable group selected from [See Original Patent for Chemical Structure Diagram]

where

R<26 > is hydrogen or C1-C4 alkyl;

T is -O- or NR<27> -, wherein R<27 > is hydrogen or a C1-C4 alkyl group or R<27 > is a group -B<7> Q<3> ;

B<7 > is a valence bond a straight or branched alkylene oxaalkylene or oligo-oxaalkylene group;

K<2 > is a group -(CH2)[q]OC(O)-, -(CH)[q]C(O)O-, -(CH2)[q]OC(O)O-, (CH2)[q]NR<20> -, -(CH2)[q]NR<> C(O)-, -(CH2)[q]C(O) NR<20> -, -(CH2)[q]NR<20> C(O)O-, -(CH2)[q]OC (O)NR<20> -, -(CH2)[q]NR<20> C(O)NR<20> - (in which the groups R<20 > are the same or different), -(CH2)[q]O-, or -(CH2)[q]SO3-, or a valence bond and group; and

Q<3 > is a reactive group selected from the group consisting of aldehyde groups; silane and siloxane groups containing one or more substituents selected from halogen atoms and C[1-4]-alkoxy groups; hydroxyl; amino; carboxyl; epoxy; -CHOHCH2Hal (in which Hal is selected from chlorine, bromine and iodine atoms); succinimido; tosylate; triflate; imidazole carbonyl amino; optionally substituted triazine groups; cinnamyl; ethylenically and acetylenically unsaturated groups; acetoacetoxy; methylol; and chloroalkylsulphone groups; acetoxy;

mesylate; carbonyl di(cycloalkyl carbodiimidoyl; and oximino.

Preferred groups Q<3 > are aldehyde, reactive silane and siloxane, amino, epoxy, CHOHCH2Hal (in which Hal is halogen), succimimido, tosylate, triflate, imidazolecarbonyl amino and optionally substituted triazine groups.

In one embodiment the present invention provides a polymer obtainable by copolymerising the zwitterionic monomer, the monomer having a reactive group and a radical polymerisable, preferably an ethylenically unsaturated, comonomer containing a radical polymerisable moiety and an alkyl group of 6 or more carbon atoms, which alkyl group optionally contains one or more etheric oxygen atoms and optionally one or more carbon-carbon double or triple bonds, or a fluoroalkyl group which optionally contains one or more etheric oxygen atoms and optionally one or more carbon-carbon double or triple bonds, or a siloxane group.

In this embodiment, the polymer is a copolymer comprising residues of a comonomer containing a physisorbable group and as well as the zwitterionic monomer and monomer having a reactive group.

It is also preferred that the physisorbable group is an alkyl or fluoroalkyl group optionally containing one or more carbon-carbon double or triple bonds. Such a group may contain one or more etheric oxygen atoms, but in an especially preferred embodiment does not contain any etheric oxygen atoms.

In one embodiment, where the physisorbable group is an alkyl or fluoroalkyl group, optionally containing one or more etheric oxygen atoms, this group does not contain any carbon-carbon double or triple bonds.

Where a hydrophillic surface having functional groups is to be coated, groups capable of covalently binding the polymer to the surface may be incorporated into the polymer as pendant groups.

Where a surface bearing an ionic charge is to be coated, ionic groups, capable of binding the polymer to the surface by ionic interactions, may be incorporated into the polymer of the invention as pendant groups.

According to a preferred embodiment, the invention therefore provides a polymer obtainable by copolymerising the zwitterionic monomer, the monomer having a reactive group and a radical polymerisable, preferably ethylenically unsaturated, comonomer bearing an ionic group capable of binding to a surface by ionic interaction.

Optionally, in any of the above embodiments, the polymers also comprise residues of one or more diluent monomers.

The invention also provides a process for producing such a polymer which comprises polymerising such monomers and a process for coating a surface with such a polymer, for instance a process comprising the steps of (a) polymerising such monomers to form the polymer and (b) coating the surface with the polymer so formed. Optionally, the process further comprises attaching a ligand to the polymer either in solution before coating the surface, or, more preferably when coated on the surface.

In a specific embodiment the invention further provides such polymers containing residues of a crosslinkable monomer, which are uncrosslinked, when either coated on a surface or not coated on a surface and such polymers which are crosslinked when coated on a surface. The invention further provides a process of crosslinking such polymers when coated on a surface.

As yet a further feature, the present invention provides certain new monomers useful in producing the polymers of the invention.

Monomers and comonomers which may be used in the polymers of the invention will now be described in more detail.

It is to be understood that throughout the specification (alk)acrylate, (alk)acrylic and (alk) acrylamide mean acrylate or alkacrylate, acrylic or alkacrylic and acrylamide or alkacrylamide respectively. Preferably unless otherwise stated alkacrylate, alkacrylic and alkacrylamide groups contain from 1 to 4 carbon atoms in the alkyl group thereof and are most preferably methacrylate, methacrylic or methacrylamide groups. Similarly (meth)acrylate, (meth)acrylic and (meth)acrylamide shall be understood to mean acrylate or methacrylate, acrylic or methacrylic and acrylamide or methacrylamide respectively.

Zwitterionic Monomers

The zwitterionic monomer (or comonomer) bears a centre of permanent positive charge and also a centre of negative charge. Typically the centre of permanent positive charge is provided by a quaternary nitrogen atom.

Preferred comonomers which bear a centre of positive charge are of general formula (I)

Y-B-X(I)

wherein

B is a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene chain optionally containing one or more fluorine atoms up to and including perfluorinated chains or, if X contains a carbon-carbon chain between B and the centre of permanent positive charge or if Y contains a terminal carbon atom bonded to B, a valence bond;

X is a zwitterionic group and

Y is an ethylenically unsaturated polymerisable group selected from [See Original Patent for Chemical Structure Diagram]

wherein:

R is hydrogen or a C1-C4 alkyl group;

A is -O- or -NR<1> - where R<1 > is hydrogen or a C1-C4alkyl group or R<1 > is -B-X where B and X are as defined above; and

K is a group -(CH2)[p]OC(O)-, -(CH2)[p]C(O)O-, -(CH2)[p]OC(O)O-, -(CH2)[p]NR<2> -, -(CH2)[p]NR<2> C(O)-, -(CH2)[p]C(O)NR<2> -, -(CH2)[p]NR<2> C(O)O-, -(CH2)[p]OC(O) NR<2> -, -(CH2)[p]NR<2> C(O)NR<2> -, (in which the groups R<2 > are the same or different) -(CH2)[p]O-, -(CH2)[p]SO3-, or, optionally in combination with B, a valence bond and p is from 1 to 12 and R<2 > is hydrogen or a C1-C4 alkyl group.

The proviso on whether B may be a valence bond ensures that the zwitterionic group X is not directly bonded to a heteroatom, such as an oxygen or nitrogen atom in Y.

Preferred zwitterionic monomers containing a group bearing a centre of permanent positive charge are therefore of general formula (II) or (III). [See Original Patent for Chemical Structure Diagram]

where

R, A, B, K and X are as defined with reference to formula (I).

Preferably in the compounds of formula (II) R is hydrogen, methyl, or ethyl, more preferably methyl, so that (II) is an acrylic acid, methacrylic acid or ethacrylic acid derivative.

In the compounds of formula (III) K may be a valence bond and B a group, K may be a group and B a valence bond, both K and B may be groups, or K and B may together be a valence bond.

Preferably B is a group where K is a valence bond.

Where K is a group then preferably p is from 1 to 6, more preferably 1,2 or 3 and most preferably p is 1. When K is a group -(CH2)[p]NR<2> -, -(CH2)[p]NR<2> C(O)-, -(CH2)[p]C(O)NR<2> , -(CH2)[p]NR<2> C(O)O-, -(CH2)[p]OC(O)NR<2> - or -(CH2)[p]NR<2> C(O)NR<2> - then R<2 > is preferably hydrogen, methyl or ethyl, more preferably hydrogen.

In the compounds of formula (III) preferably the vinyl group is para to the group -K-B-X.

Preferably B is:

an alkylene group of formula -(CR<3> 2)[a]-, wherein the groups -(CR<3> 2)[a]- are the same or different, and in each group -(CR<3> 2)[a]- the groups R<3 > are the same or different and each group R<3 > is hydrogen, fluorine or C[1-4]alkyl or fluroalkyl, preferably hydrogen, and a is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety, more preferably -CH2O(CH2)4-; or

an oligo-oxaalkylene group of formula -[(CR<4> 2)[b]O][c](CR<4> 2)[b]- where the groups -(CR<4> 2)- are the same or different and in each group -(CR<4> 2)- the groups R<4 > are the same or different and each group R<4 > is hydrogen, fluorine or C[1-4]alkyl or fluoroalkyl, preferably hydrogen, and b is from 1 to 6, preferably 2 or 3 and c is from 2 to 11, preferably 2 to 5; or

if X contains a carbon-carbon chain between B and the zwitterionic group if Y contains a terminal carbon atom, a valence bond.

Preferred groups B include alkylene, oxaalkylene and oligo-oxaalkylene groups of up to 12 carbon atoms optionally containing one or more fluorine atoms. Where the polymer is not intended for coating a hydrophobic surface, and therefore is not intended to be bound by physiosorption to a surface, then preferably B is an alkylene, oxaalkylene or oligo-oxaalkylene group which does not contain any fluorine atoms.

In compounds of formula (III) it is preferred that K and B contain up to 12 carbon atoms in total.

Preferred groups X containing a zwitterionic group, are the groups of formula (IVB), (IVC), (IVD), (IVE) and (IVF) as defined below: monomers containing such groups may be used in combination with further monomers containing groups capable of binding to a surface, to provide a copolymer of the invention. Of these groups of formula-(IVC) are particularly preferred.

The groups of formula (IVB) are: [See Original Patent for Chemical Structure Diagram]

where

the groups R<6 > are the same or different and each is hydrogen or C[1-4]alkyl and d is from 2 to 4.

Preferably the groups R<6 > are the same. It is also preferable that at least one of the groups R<6 > is methyl, and more preferable that the groups R<6 > are both methyl.

Preferably d is 2 or 3, more preferably 3.

When X is a group of formula (IVB) preferably B is a group of formula -(CR<3> 2)- or -(CR<3> 2) eg. -(CH2)- or -(CH2CH2)-.

The groups of formula (IVC) are: [See Original Patent for Chemical Structure Diagram]

where

the groups R<7 > are the same or different and each is hydrogen or C[1-4]alkyl, and e is from 1 to 4.

Preferably the groups R<7 > are the same. It is also preferable that at least one of the groups R<7 > is methyl, and more preferable that the groups R<7 > are all methyl.

Preferably e is 2 or 3, more preferably 2. When X is a group of formula (IVC) preferably B is a group of formula -(CR<3> 2)- or -(CR<3> 2)2-, eg. -(CH2)- or -(CH2CH2)-.

The groups of formula (IVD) are: [See Original Patent for Chemical Structure Diagram]

wherein

the groups R<8 > are the same or different and each is hydrogen or C[1-4]alkyl, R<8> - is hydrogen or, more preferably, a group -C(O)B<1> R<8b > where R<8b > is hydrogen or methyl, preferably methyl, B<1 > is a valence bond or straight or branched alkylene, oxaalkylene or oligo-oxaalkalyene group, and f is from 1 to 4; and

if B is other than a valence bond Z is 1 and if B is a valence bond Z is 0, if X is directly bonded to an oxygen or nitrogen atom and otherwise Z is 1.

Preferably the groups R<8 > are the same. It is also preferable that at least one of the groups R<8 > is methyl, and more preferable that the groups R<8 > are all methyl.

Preferably f is 1 or 2, more preferably 2.

Preferably B<1 > is:

a valence bond;

an alkylene group of formula -(CR<3a> 2)[aa]-, wherein the groups -(CR<3a> 2)- are the same or different, and in each group (CR<3a> 2)- the groups R<3a> - are the same or different and each group R<3a> - is hydrogen or C[1-4]alkyl, preferably hydrogen, and aa is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety, more preferably -CH2O(CH2)4-; or

an oligo-oxaalkylene group of formula -[(CR<4a> 2)[ba]O][ca]- where the groups -(CR<4a> 2)- are the same or different and in each group -(CR<4a> 2)- the groups R<4a > are the same or different and each group R<4a > is hydrogen or C[1-4]alkyl, preferably hydrogen, and ba is from 1 to 6, preferably 2 or 3, and ca is from 1 to 12, preferably 1 to 6.

Preferred groups B<1 > include a valence bond and alkylene, oxaalkylene and oligo-

oxaalkylene groups of up to 12 carbon atoms.

Preferably B and B<1 > are the same.

When X is a group of formula (IVD) preferably B is a group of formula -[(CR<4> 2CR<4> 2)[c]O[b]]CR<4> 2CR<4> 2-, eg. -(CH2CH2O) (CH2CH2)-.

The groups of formula (IVE) are: [See Original Patent for Chemical Structure Diagram]

wherein

the groups R<9 > are the same or different and each is hydrogen or C1-C4 alkyl, R<9a > is a hydrogen or, more preferably, a group -C(O)B<2> R[9b], R<9b > is hydrogen or methyl, preferably methyl, B<2 > is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group, and g is from 1 to 4; and

if B is other than a valence bond Z is 1 and if B is a valence bond Z is 0 if X is directly bonded to an oxygen or nitrogen atom and otherwise Z is 1.

Preferably the groups R are the same. It is also preferable that at least one of the groups R<9 > is methyl, and more preferable that the groups R<9 > are all methyl.

Preferably g is 1 or 2, more preferably 2.

Preferably B is:

a valence bond;

an alkylene group of formula (CR<3a> 2)[ab]-, wherein the groups -(CR<3b> 2)- are the same or different, and in each group -(CR<3b> 2)- the groups R<3b > are the same of different and each group R<3b> - is hydrogen or C[1-4]alkyl, preferably hydrogen, and ab is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6, carbon atoms in each alkyl moiety, more preferably -CH2O(CH2)4-; or

an oligo-oxaalkylene group of formula -(CR<4b> 2)[bb]O][cb]- where the groups -(CR<4b> 2)- are the same or different and in each group -(CR<4b> 2)- the groups R<4b > are the same or different and each group R<4b > is hydrogen or C[1-4]alkyl, preferably hydrogen, and bb is from 1 to 6, preferably 2 or 3, and cb is from 1 to 12, preferably 1 to 6.

Preferred groups B<2 > include a valence bond and alkylene, oxalkylene and oligo-oxalkylene groups of up to 12 carbon atoms.

Preferably B and B<2 > are the same.

When X is a group of formula (IVE) preferably B is a group of formula -[(CR<4> 2CR<4> 2)[b]O][c]CR<4> 2CR<4> 2-, eg. -(CH2CH2O)[c]CH2CH2-.

The groups of formula (IVF) are: [See Original Patent for Chemical Structure Diagram]

wherein

the groups R<10 > are the same or different and each is hydrogen or C[1-4]alkyl, R<10a > is hydrogen or, more preferably, a group -C(O)B<3 > R<10b > where R<10b > is hydrogen or methyl, preferably methyl, B<3 > is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group, and h is from 1 to 4; and

if B is other than a valence bond Z is 1 and if B is a valence bond Z is 0 if X is directly bonded to the oxygen or nitrogen and otherwise Z is 1.

Preferably the groups R<10 > are the same. It is also preferable that at least one of the groups R<10 > is methyl, and more preferable that the groups R<10 > are all methyl.

Preferably h is 1 or 2, more preferably 2.

Preferably B<3 > is:

a valence bond;

an alkylene group of formula -(CR<3c> 2)[ac]-, wherein the groups -(CR<3c> 2)- are the same or different and in each group (CR<3c> 2)- the groups R<3c > are the same or different and each group R<3c > is hydrogen or C[1-4]alkyl, preferably hydrogen, and ac is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety, more preferably -CH2O(CH2)4-; or

an-oligo-oxaalkylene group of formula -[(CR<4c> 2)[bc]O][cc]- where the groups -(CR<4c> 2)- are the same or different and in each group -(CR<4c> 2)- the groups R<4c > are the same or different and each group R<4c > is hydrogen or C[1-4]alkyl, preferably hydrogen, and bc is from 1 to 6, preferably 2 or 3, and cc is from 1 to 12, preferably 1 to 6.

Preferred groups B<3 > include a valence bond and alkylene, oxaalkylene and oligo-oxaalkylene groups of up to 12 carbon atoms.

Preferably B and B<3 > are the same.

When X is a group of formula (IVF) preferably B is a group of formula -[(CR<4> 2CR<4> 2)[b]O][c]CR<4> 2CR<4> 2-, eg. -(CH2CH2)[c]CH2CH2-.

Particular examples of preferred zwitterionic monomers are 2(methacryloyloxy)ethyl-2'(trimethylammonium)ethyl phosphate inner salt and 1[4(4'-vinylbenzyloxy)butane] 2"(trimethylammonium)ethyl phosphate inner salt.

Zwitterionic monomers, such as those of formula (II) and (III) may be prepared by conventional techniques using known reactions, for example using a suitable substituted alkyl (alk)acrylate or suitable substituted styrene as precursor. Examples of suitable substituted alkyl (alk)acrylates include dimethylaminoethyl(meth)acrylate and 2-hydroxyethyl(meth) acrylate.

Monomers of formula (II) or (III) containing a group of formula (IVB) or (IVC) may be prepared as described in Reference Example 1 to 3 or by analogous known methods.

Monomers of formula (II) or (III) containing a group of formula (IVD) in which R<8a > is -C(O)B<1> R<8b > may be prepared by selective acylation of glycerophosphorylcholine or analogues thereof at the primary hydroxyl group with an activated acid derivative such as an acid anhydride O(C(O)B<1> R<8b>)2 or an acid halide R<8b> B<1> COHal where B<1 > and R<8b > are as defined above and Hal is halogen, followed by acylation of the secondary hydroxyl group with an appropriate acylating agent, for example methacryloyl chloride. Purification, for example by column chromatography on a suitable support, may be performed after each acylation or after the second acylation only. Suitable activated acid derivatives include acid anhydrides, acid halides, reactive esters and imidazolides. The acylations may be performed in a suitable anhydrous, aprotic solvent, for example N,N-dimethylformamide,

optionally in the presence of a suitable non-nucleophilic base, for example triethylamine.

Alternatively, the primary alcohol group in glycerophosphoryl choline or an analogue thereof may be blocked by reaction with a suitable protecting group reagent, for example t-butyldimethylsilyl chloride, under standard conditions and the secondary hydroxy group then treated with an acylating agent such as methacryloyl chloride. The t-butyldimethylsilyl protecting group may be removed by treatment with a dilute organic or mineral acid, for example p-toluene sulphonic acid, hydrochloric acid or with tetra-butylammonium fluoride. The deblocked primary hydroxyl group may then be treated with an activated acid derivative such as an acid anhydride O(C(O)B<1> R<8b>)2 or acid halide R<8b> B<1> COHal where B<1 > and R<8b > are as defined above, and Hal is halogen.

Analogues of glycerophosphorylcholine (compounds of formula (II) or (III) containing a group (IVD) where R<8a > is hydrogen) may be prepared by reaction of phosphorus oxychloride with a bromoalcohol in an inert aprotic solvent, such as dichloromethane, to give a bromoalkylphosphorodichloridate. The dichloro derivative thus produced may then be treated with an appropriately protected glycerol derivative, for example 2,2-dimethyl 1,3-dioxolane-4-methanol, in the presence of a base, for example triethylamine, followed by acid hydrolysis to give a bromoalkylphosphoroglycerol derivative. This may then be treated with an amine NR<8> 3, where R<8 > is as defined above, for example trimethylamine, to generate the glycerophosphorylcholine analogue. This preparation is depicted in the following scheme. [See Original Patent for Chemical Structure Diagram]

where

R<8 > and f are as defined in relation to groups of formula (IVD).

Monomers of formula (II) or (III) containing a group of formula (IVE) in which R<9a > is -C (O)B<2> R<9b > may be prepared by the selective acylation of glycerophosphorylcholine or an analogue thereof at the primary hydroxyl group with for example, methacryloyl chloride followed by reaction at the secondary hydroxyl group using an activated acid derivative, such as an acid halide O(C(O)B<2> R<9b>)2 or an acid halide R<9b> B<2> COHal, where B<2 > and R<5b > are as defined above and Hal is halogen. The intermediates and final products may be purified, as necessary using column chromatography. Optionally, protecting group strategy, similar to that outlined above in relation to production of monomers containing a group of formula (IVD) may be employed.

Monomers of formula (II) or (III) containing a group of formula (IVF) may be prepared in an analogous manner to monomers containing groups of formula (IVD) or (IVE).

Comonomers Capable of Stably Binding a Polymer to a Surface

The polymer of the invention comprises residues of comonomer containing a group capable of stably binding a polymer at a surface which is a group capable of forming covalent bonds with a coreactive group at the surface and/or cross-linking the polymer as well as the residues of the comonomer containing a zwitterionic group.

As has already been mentioned, the nature of the group capable of binding to a surface, and therefore the nature of the comonomers containing such groups, will depend upon the nature of the surface which is to be coated with the polymer. The various types of such comonomers will now be described.

It will be appreciated that in some circumstances it may be desirable to use a combination of different comonomers containing groups capable of binding to a surface. Preferably a comonomer of type a), b) and/or c) as defined below or a combination of such comonomers is used, more preferably a comonomer of types b) is used with a comonomer of a) or c).

a) Comonomers containing an alkyl, fluoroalkyl or siloxane group

The comonomers containing an alkyl, fluoroalkyl or siloxane group, which are suitable for providing binding to a hydrophobic surface, are comonomers containing an alkyl group of 6 or more carbon atoms which group optionally contains one or more etheric oxygen atoms and optionally one or more carbon-carbon double or triple bonds or a fluoroalkyl group, preferably of 6 or more carbon atoms, which group optionally contains one or more etheric oxygen atoms and optionally one or more carbon-carbon double or triple bonds, or containing a siloxane group, containing up to 50 silicon atoms, preferably in a linear chain.

Preferably the alkyl or fluoroalkyl groups contains up to 24 carbon atoms, for instance up to 18 carbon atoms, or containing a siloxane group, containing up to 50 silicon, preferably in a linear chain. Preferred comonomers containing an alkyl, fluoroalkyl or siloxane group are those of general formula (VI)

Y<1> -Q(VI)

where

Y<1 > is an ethylenically unsaturated polymerisable group selected from [See Original Patent for Chemical Structure Diagram]

where

R<14 > is hydrogen or C1C4 alkyl,

A' is -O- or -NR<1b> - where R<15 > is hydrogen or a C1-C4 alkyl group or R<15 > is a group Q;

K<1 > is a group -(CH2)1OC(O)-, -(CH)1C(O)O-, -(CH2)1OC(O)O-, -(CH2)1NR<16> -, -(CH2)1NR<16> C(O)-, -(CH2)1C(O)NR<16> -, -(CH2)1NR<16> C(O)O-, -(CH2)1OC(O)NR<16> -, -(CH2)1NR<16> C(O)NR<16> - (in which the groups R<16 > are the same or different), -(CH2)1O-, -(CH2)1SO3-, a valence bond and 1 is from 1 to 12 and R<16 > is hydrogen or a C1-C4 alkyl group; and

Q is

(a) a straight or branched alkyl, alkoxyalkyl or (oligo-alkoxy)alkyl chain containing 6 or more, preferably 6 to 24, carbon atoms unsubstituted or substituted by one or more fluorine atoms and optionally containing one or more carbon-carbon double or triple bonds; or

(b) a siloxane group -(CR<16a> 2)[qq](SiR<16b> 2) (OSiR<16b> 2)[PR]R<16b > in which each group R<16a > is the same or different and is hydrogen or alkyl of 1 to 4 carbon atoms or aralkyl, for example benzyl or phenethyl, each group R<16b > is alkyl of 1 to 4 carbon atoms, qq is from 1 to 6 and pp is from 0 to 49.

Preferred comonomers of formula (VI) bearing a group Q include those of formula (VII) and (VIII): [See Original Patent for Chemical Structure Diagram]

wherein:

R<14> , A', K<1 > and Q are as defined in relation to formula (VI).

Preferably in the compounds of formula (VII) R<14 > is hydrogen methyl or ethyl, more preferably methyl so that the compound of formula (VII) is preferably an acrylic acid, methacrylic acid or methacrylic acid derivative.

In the compounds of formula (VIII) K<1 > may for instance be a valence bond. Where K<1 > is a group then preferably 1 is from 1 to 6, more preferably 1, 2 or 3 and most preferably 1 is 1. When K<1 > is a group -(CH2)1NR<16> -, -(CH2)1OC(O)NR<16> -, -(CH2)1NR<16> C(O)O-, -(CH2)1NR<16> C(O)-, -(CH2)1C(O)NR<16> - or -(CH2)1NR<16> C(O)NR<16> - then R<16 > is preferably hydrogen, methyl or ethyl, more preferably hydrogen.

In the compounds of formula (VIII), preferably the vinyl group is para to the group -K<1> -Q.

Preferably Q is an alkyl or fluoroalkyl group optional] containing one or more etheric oxygen atoms and optionally or more carbon-carbon double or triple bonds. More preferably Q is:

an alkyl group of formula -(CR<17> 2)[m]CR<17> 3 wherein the groups -(CR<17> 2)- are the same or different, and in each group -(CR<17> 2) the groups R<17 > are the same or different and each group R<17 > is hydrogen, fluorine or C[1-4]alkyl or fluoroalkyl and m is from 5 to 23 if Q contains no fluorine atoms or from 1 to 23, preferably 5 to 23, if Q contains one or more fluorine atoms;

an alkoxyalkyl having 1 to 12 carbon atoms in each alkyl moiety; unsubstituted or substituted by one or more fluorine atoms; or

an (oligo-alkoxyl) alkyl group of formula -[(CR<18> 2)[n]O][o](CR<18> 2)[n]R<18 > where the groups -(CR<18> 2) are the same or different and in each group -(CR<18> 2)- the groups R<18 > are the same or different and each group R<18 > is hydrogen, fluorine or C [1-4]alkyl or fluoroalkyl and n is from 2 to 6, preferably 3 to 4, and 0 is from 1 to 12.

When Q is a group -[(CR<18> 2)[n]O][o](CR<18 > 2)[n]R<18 > wherein all the groups R<18 > are hydrogen and in all the groups -[(CR<18> 2)[n]O]- n is 2 the group of formula Q is not able to form strong secondary valence interactions with hydrophobic surfaces. Whilst residues of monomers containing such a group may be included in the polymers of the invention, it is also necessary to include residues of monomers which are capable of forming such strong secondary valence interactions if such interactions are to bind a polymer to a surface. Monomers which have groups containing oligo(higher alkylene) oxide moieties can be used to provide monomers which contain oligo -alkylene oxide moieties in which at least 50 mol % of individual alkylene oxide units contain 3 or more carbons atoms. Thus, for instance a mixed oligo(ethylene oxide/propylene oxide) side chain could be used provided that there are more propylene oxide units than ethylene oxide units.

Where Q is an (oligo-alkoxy)-alkyl group containing residues -[(CR<18> 2)[n]O]- wherein n is 2, then preferably n is 2 in no more than 50 mol % of the residues -[(CR<18> 2)[n]O]-.

Alternatively, Q may be a group in which one or more of the alkyl or alkylene moieties in such an alkyl, alkoxyalkyl or (oligoalkoxy) alkyl group is replaced by a corresponding alkenyl, alkynyl, alkenylene or alkynylene moiety.

Preferred groups Q include alkyl, alkoxyalkyl and (oligo-alkoxy)alkyl groups optionally containing one or more carbon-carbon double or triple bonds of 8 or more, more preferably 10 or more, even more preferably 12 or more, for instance 14 or more, such as 16 or more carbon atoms. Such groups may contain one or more fluorine atoms and be therefore fluoroalkyl derivatives. Preferably however, such groups do not contain any fluorine atoms.

Particularly preferred groups are straight chain alkyl or fluoroalkyl groups optionally containing one or more carbon-carbon double or triple bonds.

Where Q is a siloxane group, each group -(CR<16a> 2)- may be the same or different, preferably the same, and preferably each group R<16a > is hydrogen. Preferably qq is from 2 to 4, and is most preferably 3. Each group -(SiR<16b> 2)- may be the same or different,

preferably the same, and preferably each group R<16b > is methyl. Preferably pp is from 4 to 29. Preferred comonomers where Q is a siloxane group are those of formula (VII).

In one specific embodiment the group Q does not contain any ethylenic unsaturation, i.e. any carbon-carbon double or triple bonds.

Particular examples of comonomers containing an alkyl, fluoroalkyl or siloxane group include: n-dodecyl methacrylate, octadecyl methacrylate, hexadecyl methacrylate, 1H,1H,2H,2H-heptadecafluorodecyl methacrylate, p-octyl styrene, p-dodecyl styrene and monomethacryloxypropyl terminated siloxanes. n-Dodecyl methacrylate is particularly preferred.

Comonomers containing a physisorbable alkyl or fluoroalkyl, which does not contain a carbon-carbon double or triple bond, or a siloxane group such as those of formulae (VII) and (VIII) are commercially available or may be,prepared by conventional techniques using known reactions.

In a second specific embodiment of such comonomers, the group Q does contain ethylene unsaturation, i.e. one or more carbon-carbon double or triple bonds. Such comonomers may for example contain a vinylic, divinylic, acetylenic or diacetylenic moiety. Comonomers containing acetylenic rather than vinylic unsaturation are in general preferred, especially those containing a single acetylenic group.

Comonomers which contain such an ethylenic unsaturated group are capable of providing crosslinking between linear polymer claims once the polymer is coated onto a substrate, as well as binding to the substrate by physisorption. Such crosslinking may improve the stability of the coating and is typically formed by irradiation, for example with uv- or gamma-radiation. The crosslinking of such groups may be employed either alone or in addition to the use of a comonomer containing a reactive group as a crosslinkable comonomer as described below.

Particularly preferred crosslinkable comonomers capable of binding to a substrate by physisorption are those of formula (VIIA) and (VIIIA). [See Original Patent for Chemical Structure Diagram]

in which R<14> , A' and K<1 > are as hereinbefore defined and QQ is an alkynyl group containing 6 or more carbon atoms and one or two, preferably one, carbon-carbon triple bonds provided that the acetylenic moieties are not directly bonded to A' or K<1> .

The present invention provides, as a further feature, comonomers of formula (VIIA) and (VIIIA).

Amongst such comonomers it is preferred that QQ is an alkynyl group containing from 6 to 24 carbon atoms, preferably 8 or more, more preferably 10 or more, even more preferably 12 or more, for instance 14 or more, such as 16 or more carbon atoms.

It is also preferred that the group QQ does not contain a terminal acetylenic moiety, i.e. a group -C- SYMBOL OMITTED CH.

A particularly preferred group QQ is 7-dodecynyl and a specific example of a compound of formula (VIIA) containing such a group is dodec-7-yn-1-ol methacrylate.

The compound of formula (VIIA) and (VIIIA) and other comonomers of formula (VII) and (VIII) containing an ethylenically unsaturated physisorbable group Q, may be prepared by anology with known methods. Their preparation is illustrated by Reference Example 2.

b) Comonomers bearing a reactive group

Preferred comonomers, which are suitable for providing binding to a hydrophillic surface having functional groups, contain a reactive group capable of covalently binding to a 2S surface and are of general formula (IX)

Y2-Q<1(IX)>

where

Y<2 > is an ethylenically unsaturated polymerisable group selected from [See Original Patent for Chemical Structure Diagram]

where

R<19 > is hydrogen or C1-C4 alkyl,

K<2 > is a group -(CH2)[q]OC(O)-, -(CH)[q]C(O)O-, -(CH2)[q]OC(O)O-, -(CH2)[q]NR<20> -, -(CH2)[q]NR<20> C(O)-, -(CH2)[q]C(O)NR<20> -, -(CH2)[q]NR<20> C(O)O-, -(CH2)[q]OC(O)NR<20> -, -(CH2)[q]NR<20> C(O)NR<20> - (in which the groups R<20 > are the same or different), -(CH2)[q]O-, or -(CH2)[q]SO3-, or a valence bond and q is from 1 to 12 and R<20 > is hydrogen or a C1-C4 alkyl group; and

Q<1 > is a reactive group capable of reacting to provide covalent binding to a surface.

Preferred comonomers of formula (IX) bearing a reactive group Q<1 > include those of formula (X) and (XI) defined below.

The compounds of formula (X) are: [See Original Patent for Chemical Structure Diagram]

wherein:

R<19 > is as defined with reference to formula (X), and Q<2 > is a reactive group.

Preferably in the compounds of formula (X) R<19 > is hydrogen, methyl or ethyl, more preferably methyl, so that the compound of formula (X) is preferably an acrylic acid, methacrylic acid or ethacrylic acid derivative.

Preferably Q<2 > is hydrogen, or more preferably -OH or a group of the formula:

-T-B<7> -Q<3>

where

T is -O-, or -NR<21> - where R<21 > is hydrogen, C1-C4 alkyl or a group -B<7> -Q<3> ;

B<7 > is a valence bond or, more preferably, a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene chain; and

Q<3 > is a reactive group capable of reacting to provide covalent binding to a surface such as an aldehyde group or a silane or siloxane group containing one or more reactive substituents such as halogen, for example chlorine, or alkoxy, generally containing from 1 to 4 carbon atoms, for example methoxy or ethoxy, or, more preferably Q<3 > is a hydroxyl, amino, carboxyl, epoxy, -CHOHCH2Hal, (in which Hal is a halogen atom such as chlorine, bromine or iodine) succinimido, tosylate such as 2(N-methylpyridinium) tosylate, triflate, imidazole carbonyl-amino, or an optionally substituted triazine group. Q<3 > can also be cinnamyl; ethylenically and acetylenically unsaturated groups; acetoacetoxy; methylol; and chloroalkylsulphone groups; acetoxy; mesylate; carbonyl di(cycloalkyl carbodiimidoyl; and

oximino.

Preferably B<7 > is:

an alkylene group of formula -(CR<22> 2)[r]-, wherein the groups -(CR<22> 2)- are the same or different, and in each group -(CR<22> 2)- the groups R<22 > are the same or different and each group R<22 > is hydrogen or C[1-4]alkyl, preferably hydrogen, and r is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety; or

an oligo-oxaalkylene group of formula -[(CR<23> 2)[s]O][t](CR<23> 2)[s]- where the groups -(CR<23> 1)- are the same or different and in each group -(CR<23> 2)- the groups R<23 > are the same or different and each group R<23 > is hydrogen or C[1-4]alkyl, preferably hydrogen, and s is from 1 to 6, preferably 2 or 3, and t is from 1 to 11, preferably 1 to 5.

Preferred groups B<7 > include alkylene, oxaalkylene and oligo-oxaalkylene groups of up to 12 carbon atoms.

Where Q<3 > is a silane or siloxy group, preferably B<7 > is an alkylene group of 1 to 6, preferably 2 to 4, more preferably 3 s carbon atoms.

Particular examples of the group B<7 > are -CH2-, -CH2CH2- and -(CH2)6-.

The compounds of formula (XI) are: [See Original Patent for Chemical Structure Diagram]

wherein

K<2> , B<7 > and Q<3 > are as defined in relation to formula (IX)

In the compounds of formula (XI) preferably the vinyl group is para to the group -K<2> -B<7> Q<3> .

K<2 > may for instance be a valence bond. Where K<2 > is a group then preferably q is from 1 to 6, more preferably 1,2 or 3 and most preferably q is 1. When K<2 > is a group -(CH2)[q]NR<20> -, -(CH2)[q]OC(O)NR<20> , -(CH2)[q]NR<20> C(O)O-, -(CH2)[q]NR<20> C(O)-, -(CH2)[q]C(O)NR<20> - or -(CH2)[q]NR<20> C(O)NR<20> - then R<20 > is preferably hydrogen, methyl or ethyl, more preferably hydrogen.

Particular examples of comonomers bearing a reactive group include chloromethylstyrene, methacrylic acid, 2-aminoethylmethacrylate, 2,3-epoxypropyl methacrylate, 3-chloro-2-hydroxypropylmethacrylate, 2-methacryloyloxy-ethyl dichlorotriazine, 3-chloro-2-hydroxy-propylmethacrylamide and glycidyl methacrylate and reactive methacrylate esters containing the group HetC(O)O- in which (Het) is a heterocyclic ring, for example benzotriazole or imidazole and reactive methacrylate esters containing a group R<16> OC(O)- in which R<16 > is a succinimido or pentafluorophenyl group.

Particularly preferred comonomers bearing reactive groups are 2-aminoethyl-methacrylate and 3-chloro-2-hydroxypropylmethacrylate.

Comonomers bearing a reactive group capable of binding covalently to a surface, such as those of formula (X) or (XI), are commercially available or may be prepared by conventional techniques using known reactions.

Comonomers of formula (X), which are dichlorotriazine monomers may be prepared in known

manner for example by reacting a substituted hydroxy-alkyl(alk)acrylate or aminoalkyl(alk) acrylate with trichlorotriazine in a suitable solvent and in the presence of a base.

Comonomers of formula (XI) which are reactive methacrylate esters in which the ester groups contains an imidazole group may be prepared in known manner by reacting a substituted hydroxyalkyl(alk)acrylate (e.g. 2-hydroxyethyl(meth)acrylate), polyethylene-oxide (meth) acrylate or polypropyleneoxide (meth)acrylate with 1,1-carbonyl-diimidazole in a dry solvent. Analogous known methods may be used to prepare succinimido and pentafluorophenyl methacrylate-esters of formula (X), by reaction with a reactive ester, acid halide or acid anhydride.

Where comonomers containing a reactive group are used to bind a copolymer to a surface by covalent bonding, it will be appreciated that not all of the reactive groups need necessarily bind to surface reactive groups and that groups not so bound may participate in other chemistry. Such groups may in particular provide points for the attachment of moieties such as ligands to the polymer, when coated onto a substrate.

Comonomers containing a reactive group, such as compounds of formula (X) and (XI) may be used as comonomers containing crosslinkable groups, which react with other crosslinkable groups, rather than a monomer which bind covalently to a surface.

Where comonomers containing a reactive group are used to provide such crosslinkable groups then the crosslinkable groups and/or the copolymerisation conditions will be chosen so that they will not crosslink when the comonomers are copolymerised; thus the polymerisation product will be an uncrosslinked linear copolymer which may be subsequently crosslinked after coating the copolymer onto a surface so as to improve the stability of the coating. When such crosslinking between linear polymer chains is employed the crosslinkage may be formed either between two such crosslinkable groups or between a crosslinkable group and a non-inert group in a diluent comonomer residue (defined later). Such a crosslinkage may be formed either by direct reaction of the groups forming the crosslinkage or by reaction of these groups with a reactive bridging molelcule for example a reactive gas, such as ammonia.

Residues of such comonomers may therefore be present in polymers which are designed to coat hydrophobic surfaces and containing residues of a zwitterionic monomer and a comonomer containing an alkyl, fluoroalkyl or siloxane group, which is of formula (VII) or (VIII). Similarly residues of such comonomers may also be present in polymers designed to bind to a surface by ionic interaction and which contains residues of a compound of formula (XIII) or (XIV) as defined below.

Preferred reactive comonomers which are used to crosslink the comonomer, rather than provide covalent binding to the surface, are those of formula (X) or (XI) in which Q<3> , or Q<4 > contains a crosslinkable cinnamyl, epoxy, -CHOHCH2Hal (in which Hal is a halogen atom), methylol, silyl, an ethylenically unsaturated crosslinkable group, such as an acetylenic, diacetylenic, vinylic or divinylic group, or an acetoacetoxy or chloroalkyl sulfone, preferably chloroethyl sulphone, group.

Particular examples of comonomers bearing a group capable of crosslinking include methacrolein, cinnamyl methacrylate, 2,3-epoxypropyl methacrylate, 3-chloro-2-hydroxypropyl methacrylate, hydroxymethyl methacrylamide, 3-(trimethoxysilyl)propyl methacrylate, 2-acetoacetoxyethyl methacrylate 3-(vinylbenzyl)-2-chloroethyl sulfone.

When a polymer of the invention, containing crosslinkable groups, is coated on a substrate the polymer is in substantially uncrosslinked form. After coating, crosslinking of crosslinkable groups may be performed to increase the strength and stability of the polymer coating.

c) Comonomers bearing an ionic group

Preferred comonomers bearing an ionic group capable of binding to a surface by ionic interaction are of general formula (XII)

Y<3> -B<9> -Q<5(XII)>

where

Y<3 > is an ethylenically unsaturated polymerisable group selected from [See Original Patent for Chemical Structure Diagram]

where

R<26 > is hydrogen or C1-C4 alkyl;

A" is -O- or -NR<27> -, wherein R<27 > is hydrogen or a C1-C4 alkyl group or R is a group -B<9> -Q<5> ;

B<9 > is a valence bond, a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group;

K<3 > is a group -(CH2)[x]OC(O)-, -(CH)[x]C(O)O-, -(CH2)[x]C(O)O-, -(CH2)[x]NR<28> -, -(CH2)[x]NR<28> C(O)-, -(CH2)[x]C(O)NR<28> -, -(CH2)[x]NR<28> C(O)O-, -(CH2)[x]OC(O)NR<28> -, -(CH2)[x]NR<28> C(O)NR<28> - (in which the groups R<28 > are the same or different), -(CH2)[x]O-, -(CH2)[x]SO3-, a valence bond (optionally in combination with B) and x is from 1 to 12 and R<28 > is hydrogen or a C1-C4 alkyl group;

Q<5 > is an ionic group capable of binding to a surface by ionic interaction.

Preferred comonomers of formula (XII) are therefore those of formula (XIII) and (XIV): [See Original Patent for Chemical Structure Diagram]

wherein:

R<26> , A", B<9> , K<3 > and Q<5 > are as defined in relation to formula (XII).

Preferably in the compounds of formula (XIII) R<26 > is hydrogen, methyl or ethyl, more preferably methyl, so that the compound of formula (XIII) is preferably an acrylic acid, methacrylic acid or ethacrylic acid derivative.

In the compounds of formula (XIV), K<3 > may for instance be a valence bond. Where K<3 > is a group then x is preferably from 1 to 6, more preferably 1, 2 or 3 and most preferably x is 1. When K<3 > is a group -(CH2)[x]NR<26> -, (CH2)[x]OC(O)NR<26> -, -(CH2)[x]NR<26> C(O)O-, -(CH2)[x]NR<26> C(O)-, -(CH2)[x]C(O)NR<26> - or -(CH2)[x]NR<26> C(O)NR<26> - then R<26 > is preferably hydrogen, methyl or ethyl, more preferably hydrogen.

In the compounds of formula (XIV) preferably the vinyl group is para to the group -K<3> -B<8> -Q<4> .

Preferably B<9 > is:

an alkylene group of formula -(CR<29> 2)[y]-, wherein the groups -(CR<28> 2)- are the same or different, and in each group -(CR<28> 2)- the groups R<29 > are the same or different and each group R<29 > is hydrogen or C[1-4]alkyl, preferably hydrogen, and y is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety; or

an oligo-oxaalkylene group of formula -[(CR<30> 2)[yy]O][xx](CR<30> [2)][yy]- where the groups -(CR<30> 2)- are the same or different and in each group -(CR<30> 2)- the groups R<30 > are the same or different and each group R<30 > is hydrogen or C[1-4]alkyl, preferably hydrogen, and yy is from 1 to 6, preferably 2 or 3, and xx is from 1 to 12, preferably 1 to 6.

Preferred groups B<9 > include alkylene, oxaalkylene and oligo-oxaalkylene groups of up to 12 carbon atoms.

Particular examples of the group B<9 > are -CH2-, -CH2CH2- and -(CH2)6-

The group Q<5 > may be either anionic or cationic depending upon the surface to be coated. Where the surface has a cationic surface charge, the group Q<5 > will be anionic and may for example be a carboxylate, sulphonate, hydrogenphosphate or phosphate group. Where the surface has an anionic surface charge, the group Q<5 > will be cationic and may for example by a group -NR<31> 3 in which each group R<31 > is the same or different, and is hydrogen or alkyl of 1 to 6 carbon atoms two of which groups R<31 > may together from a heterocyclic ring containing from 5 to 7 atoms, preferably hydrogen or methyl, a group N<(+)> Het, where Het is an unsaturated heterocyclic group such as pyridyl, substituted or unsubstituted by one or more alkyl groups of 1 to 4 carbon atoms, or a group -PR<32> 3<(+) > in which each group R<32 > is the same or different and is hydrogen or alkyl of 1 to 6 carbons atoms, two of which groups R<31 > may together form a heterocyclic ring containing from 5 to 7 atoms, preferably methyl.

Particular examples of comonomers bearing an ionic group include acrylic acid, methacrylic acid, 2-sulfoethyl methacrylate, 2-methacryloyloxyethyl phosphate, p-styrene sulfonic acid, 2-(methacryloyloxyethyl)trimethylammonium chloride, 3-aminopropyl methacrylamide, vinylbenzyl trimethylammonium chloride.

Comonomers bearing a group capable of binding a polymer to a surface by ionic interaction, such as those of formula (XIII) and (XIV) are commercially available or may be prepared by conventional techniques using known reactions.

Diluent Comonomers In addition to a) the residues of monomers containing a group bearing a centre of permanent positive charge or b) the residues of comonomers containing a group bearing a centre of permanent positive charge and comonomers which are capable of binding to a surface, the polymers of the present invention may comprise residues of a diluent comonomer.

Such diluent comonomers may be used to give the polymer the desired physical and mechanical properties. They may be of any known conventional radical polymerisable, preferably ethylenically unsaturated, type compatible with other comonomer(s).

Particular examples of diluent comonomers include alkyl(alk)acrylate preferably containing 1 to 4 carbon atoms in the alkyl group of the ester moiety, such as methyl (alk)acrylate; a dialkylamino alkyl(alk)acrylate, preferably containing 1 to 4 carbon atoms in each alkyl moiety of the amine and 1 to 4 carbon atoms in the alkylene chain, e.g. 2-(dimethylamino) ethyl(alk)acrylate; an alkyl(alk)acrylamide preferably containing 1 to 4 carbon atoms in the alkyl group of the amide moiety; a hydroxyalkyl(alk)acrylate preferably containing from 1 to 4 carbon atoms in the hydroxyalkyl moiety, e.g. a 2-hydroxyethyl(alk)acrylate; or a vinyl monomer such as an N-vinyl lactam, preferably containing from 5 to 7 atoms in the lactam ring, for instance vinyl pyrrolidone; styrene or a styrene derivative which for example is substituted on the phenyl ring by one or more alkyl groups containing from 1 to 6, preferably 1 to 4, carbon atoms, and/or by one or more halogen, such as fluorine atoms, e.g.

(pentafluorophenyl)styrene.

Other suitable diluent comonomers include polyhydroxyl, for example sugar, (alk)acrylates and (alk)acrylamides in which the alkyl group contains from 1 to 4 carbon atoms, e.g. sugar acrylates, methacrylates, ethacrylates, acrylamides, methacrylamides and ethacrylamides. Suitable sugars include glucose and sorbitol. Particularly suitable diluent comonomers include methacryloyl glucose or sorbitol methacrylate.

Further diluents which may be mentioned specifically include polymerisable alkenes, preferably of 2-4 carbon atoms, eg. ethylene, dienes such as butadiene, alkylene anhydrides such as maleic anhydride and cyano-substituted alkylenes, such as acrylonitrile.

Diluent comonomers may be obtained by conventional known methods.

Of the above diluent comonomers some are inert and act simply to modify the physical and mechanical properties of copolymers containing them. Others, and in particular the hydroxyalkyl(alk)acrylates and polyhydroxyl(alk)acrylates have a reactive role in addition to simply modifying physical and mechanical properties. Such comonomers contain functional groups, such as hydroxyl groups, which may react with a crosslinking group or may react with reactive groups in other molecules to attach them to the copolymer.

It will also be appreciated that alkyl(alk)acrylates containing 6 or more carbon atoms in the alkyl group may be regarded as either diluent comonomers or comonomers capable of binding a polymer to a surface by physisorption. In particular it should be noted that a copolymer which contains such a diluent comonomer and a reactive comonomer capable of reacting at a surface to provide covalent binding to a surface may be used to coat a hydrophillic surface, the reactive comonomer providing binding to the surface and the diluent modifying physical and mechanical properties. However, such a copolymer may also be to coat hydrophobic surfaces, in which the "diluent" monomer will act as a comonomer capable of binding to the surface by physisorption and the comonomer capable of covalent binding will act as a crosslinkable comonomer.

According to a feature of the present invention polymers of the invention may be prepared by copolymerising a zwitterionic comonomer optionally a further comonomer containing a group capable of stably binding the polymer to a surface, a monomer having a reactive group and a diluent comonomer.

Any conventional technique may be used for polymerisation, typically thermal or photochemical polymerisation. Where comonomers capable of producing crosslinking in the coated polymer film are present, the polymerisation condition are set such that crosslinking does not occur during polymerisation. Thus, for example, actinic radiation would not be used to prepare a polymer containing a comonomer which can form crosslinks by exposure to actinic radiation.

For thermal polymerisation a temperature from 40 to 100o C., typically 50 to 80o C. is used. For photochemical polymerisation actinic radiation such as gamma, U.V., Visible or microwave radiation may be used. Typically U.V. radiation of wavelength 200 to 400 nm is used.

The polymerisation is generally performed in a reaction medium, which is for instance a solution or dispersion using as a solvent for example acetonitrile, dimethyl formamide, chloroform, dichloromethane, ethyl acetate, dimethyl sulphoxide, dioxane, benzene, toluene, tetrahydrofuran, or where the polymer does not contain groups which react with protic solvents, water or an alkanol containing from 1 to 4 carbon atoms, e.g. methanol, ethanol or propan-2-ol. Alternatively, a mixture of any of the above solvents may be used.

The polymerisation may be carried out in the presence of one or more polymerisation

initiators, such as benzoyl peroxide, 2,2'-azo-bis(2-methylpropionitrile) or benzoin methyl ether. Other polymerisation initiators which may be used are disclosed in "Polymer Handbook", 3rd edition, Ed. J. Brandrup and E. H. Immergut, Pub. Wiley-Interscience, New York, 1989.

Generally the copolymerisation is performed for 1 to 72 hours, preferably 8 to 48, for instance 16 to 24 hours, and under an inert atmosphere of for example nitrogen or argon. The polymer is generally purified by dialysis, precipitation in a non-solvent (e.g. diethyl ether or acetone) or ultrafiltration. The resulting polymer is generally dried under vacuum, eg. for 5 to 72 hours and has a molecular weight from 10,000 to 10 million, preferably from 20,000 to 1 million.

The precise proportion and nature of the various comonomers used to prepare a copolymer according to the present invention comprising residues of a zwitterionic monomer and a comonomer containing a reactive group and optionally a further comonomer having a group capable of stably binding the polymer to a surface may be adjusted to provide a copolymer which is particularly suitable for coating a particular surface. Thus the proportion of comonomer containing a group capable of stably binding the polymer to a surface may be adapted to provide efficient physisorption at a particular hydrophobic surface, to correspond to the number of functional groups at a particular surface or to provide efficient binding by ionic interaction with a particular surface. Similarly the proportion of the zwitterionic monomer and of diluent and/or crosslinkable comonomer may be adapted to provide the desired biocompatibility and physical and mechanical properties. It will be appreciated that to obtain the desired combination of properties more than one type of zwitterionic monomer, comonomer containing a group capable of stably binding the polymer to a surface or crosslinkable and/or diluent comonomer may be used.

The monomer composition which is subjected to polymerisation to provide a polymer according to the invention comprises a minimum of 0.01%, preferably 1%, more preferably 5% by weight of zwitterionic monomer and a maximum of 99.9%, preferably 99%, more preferably 95% by weight of other monomer or monomers. Such other monomer or monomers may be a monomer or monomers containing a group capable of stably binding the polymer to a surface, a diluent monomer or monomers and/or a crosslinkable monomer or monomers.

The monomer composition further comprises a minimum of 0.01%, preferably 1%, more preferably 5% by weight of monomer or monomers containing a group capable of stably binding the polymer to a surface and a maximum of 99.9%, preferably 99%, more preferably 95% by weight of other monomer or monomers. Such other monomer or monomers may be a monomer or monomers containing a group bearing a centre of permanent positive charge, a diluent monomer or monomers and/or a crosslinkable monomer or monomers.

Where the polymer is to bind to a surface by physisorption then preferably the monomer composition comprises no more than 95%, more preferably no more than 90% and even more preferably no more than 80% by weight of monomer or monomers containing an alkyl, fluoroalkyl or siloxane group which is capable of binding the polymer to a surface by physisorption the balance of the composition being zwitterionic monomer, diluent monomer and/or crosslinkable monomer. Such a composition typically comprises up to 50% by weight of diluent comonomer or comonomers. Where diluent comonomer is present, it preferably comprises at least 1%, more preferably 5%, by weight of the total comonomer composition. Where present, crosslinkable comonomer or comonomers generally comprise from 0.1% to 20% by weight of the total comonomer composition.

Preferably the molar ratio in a copolymer containing a hydrophobic comonomer of zwitterionic monomer to comonomer containing an alkyl, fluoroalkyl or siloxane group capable of binding the polymer to a surface by physisorption is from 5:95 to 80:20, more preferably 10:90 to 50:50. In addition the copolymer preferably comprises from 5% to 50%, more preferably

10% to 25%, by mole residues of diluent monomer and/or from 0.1 to 20%, more preferably 1% to 10%, by mole residues of crosslinkable comonomer, provided that where residues of both diluent and crosslinkable comonomer are present, they do not exceed in combination 50%, preferably 35% by mole.

Where the polymer is to bind covalently to a surface then preferably the monomer composition comprises no more than 25%, more preferably up to 20% and even more preferably up to 15% by weight of monomer containing a group capable of binding the polymer to a surface covalently; the balance of the composition being zwitterionic monomer, and optionally diluent monomer or monomers. Such a composition typically comprises up to 95%, preferably to 90%, by weight of diluent comonomer or comonomers. Where diluent comonomer is present, it preferably comprises at least 5%, more preferably 10%, by weight of the total comonomer composition.

Preferably the molar ratio in the copolymer of zwitterionic monomer comonomer containing a reactive group capable of binding the polymer to a surface by covalent bonding is from 5:95 to 95:5, more preferably 50:50 to 90:10. In addition, the copolymer preferably comprises from 5% to 50%, more preferably 10% to 25%, by mole residues of diluent monomer and/or from 0.1% to 20%, more preferably 1% to 10%, by mole residues of crosslinkable comononer, provided that where residues of both diluent and crosslinkable comonomer are present, they do not exceed in combination 50%, preferably 35% by mole.

Where the polymer is to bind to a surface by ionic interaction, then preferably the molar ratio in the copolymer of zwitterionic monomer to comonomer containing an ionic group capable of binding the polymer to a surface by ionic interactions is from 5:95 to 95:5, more preferably 50:50 to 90:10. In addition, the copolymer preferably comprises from 5% to 50%, more preferably 10% to 25%, by mole residues of diluent monomer and/or from 0.1% to 20%, more preferably 1% to 10%, by mole residues of crosslinkable comonomer, provided that where residues of both diluent and crosslinkable comonomer are present, they do not exceed in combination 50%, preferably 35% by mole.

In addition the monomer composition may comprise further components such as a polymerisation initiator, chain transfer agent, acid, base, surfactant, emulsifier or catalyst of conventional type each in an amount from 0.1% to 5%, typically from 0.2% to 3% and preferably about 0.5%, by weight each relative to the total weight of the monomers.

As a further feature the present invention provides a process for biocompatibilising a surface which comprises coating the surface with a polymer according to the present invention. Various types of surfaces may be coated depending upon the nature of the groups in the polymer capable of binding it to the surface.

Polymers containing residues of monomers containing alkyl, fluoroalkyl or siloxane groups capable of binding the polymer to a surface by physisorption are particularly suitable for coating hydrophobic surfaces, e.g. polyethylene, polypropylene and polytetrafluoroethylene (PTFE) surfaces; fluorine containing polymers of the invention being particularly suited to coating PTFE surfaces.

Hydrophillic surfaces may be rendered hydrophobic and suitable for coating with such polymers by known methods (see for example "Chemical Reactions of Polymers" Ed. E. M. Fettes, 1964, Interscience, London).

Treatment with such a polymer is generally carried out by coating the surface with a solution, dispersion (including a microdispersion) of the polymer, generally in an alcoholic, aqueous, organic or halogenated solvent or a mixture thereof, e.g. methanol, ethanol, dichloromethane or freon. The treatment is generally carried out at ambient or elevated temperature, such as from 5 to 60o C.

In one specific embodiment of the invention, the copolymer is coated onto the substrate in the form of a microdispersion for example a microemulsion.

After coating the polymer may be crosslinked if it contains the residues of crosslinkable comonomer by known method for crosslinking the specific crosslinkable groups which are present. Crosslinking may, for instance, be introduced thermally, using actinic radiation, using reactive gases for example ammonia by changing the pH, using difunctional additives or by using activation chemistries for example by known methods as described in "Methods in Enzymology, volume 135, Immobilised Enzymes and Cells, part B", Ed. K. Mosbach, Academic Press Inc, New York, 1987. This activation may be performed on the dry coating, in the cases of thermal radiation or gas treatment. Alternatively for cases where the pH needs to be changed or additives need to be included, activation may be performed on the coated material in a solution which does not remove the coating.

Surfaces having functional groups such as hydroxyl, carboxyl or amino groups are particularly suitable for treatment with polymers according to the invention comprising residues of monomer containing a group capable of binding the polymer to a surface covalently.

Where necessary the surface of the substrate may be functionalised prior to treatment. For surfaces which do not have functional groups it is necessary to introduce these groups at the surface before treatment with the polymer. This can be effected by known etching or derivatising techniques, such as plasma discharge, which introduce the appropriate surface functionality (see for example "Chemical Reactions of Polymers" Ed. E. M. Fettes, 1964, Interscience, London).

In certain cases it is also necessary to activate functional groups at the surface of the substrate and/or the reactive groups of the polymer of the invention. This may be achieved by known means using a known activating agent for example a carbodiimide such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. Other suitable activating agents are disclosed in "Methods in Enzymology", supra. It will be appreciated that corresponding methods of activation of groups on a polymer may also be used to attach moieties, such as ligands to the polymer when coated on a substrate.

Treatment with such a polymer is generally carried out by treating the surface with a solution of the polymer, generally an alcoholic, aqueous alcoholic or aqueous solution. The treatment is generally carried out at a temperature from -5 to 50o C., for from 0.1 to 24 hours and at a pH from 2 to 13.

Surfaces having ionic groups such as carboxyl, sulphonate, phosphate, ammonium or phosphonium groups are particularly suitable for treatment with polymers according to the invention comprising residues of monomer containing a group capable of binding the polymer to ionic interaction.

Where necessary the surface of the substrate may be functionalised prior to treatment. For surfaces which do not have ionic groups it is necessary to introduce these groups at the surface before treatment with the polymer. This can be effected by known etching or derivatising techniques, such as plasma discharge, which introduce the appropriate surface functionality (see for example "Chemical Reactions of Polymers" Ed. E. M. Fettes, 1964, Interscience, London)

Treatment with such a polymer is generally carried out by treating the surface with a solution of the polymer, generally an alcoholic, aqueous alcoholic or aqueous solution. Treatment is generally carried out at a temperature from - 5 to 50o C., for from 0.1 to 24 hours and at a pH from 2 to 13.

Materials may be coated with polymers of the invention by known techniques, such as dip-coating, spray-coating, web-coating or spin coating.

Materials having surfaces coated according to the present invention can be used as a construction material for implants or prostheses for the human or animal body, particularly where these implants or prostheses are to come into direct physical contact with blood and where biocompatibility and particularly haemocompatibility are required e.g. in heart valves. They can also be used in the construction of membranes and other devices that are to be brought into contact with blood or other body fluids on an extra-corporeal basis, for example in heart-lung machines or artificial kidneys.

Additionally the polymers of the invention can be used to coat materials employed in down stream processing applications e.g. separation membranes and process equipment and tubing. In particular the materials of the invention can be used to modify the surface properties of biofiltration membranes in bioreactors and fermentation systems, where the membranes come into direct contact with complex biological solutions containing e.g. proteins, polysaccharides, fats and even whole cells. The polymers of the invention are particularly useful in reducing membrane fouling by the components of a process solution.

When the polymers of the present invention are used to coat the surface of a material which is then used in the construction coat of finished devices, it may be necessary to take precautionary steps to ensure that the coated surface is not damaged and the effectiveness of the treatment reduced before the finished device is produced.

In addition, the polymers of the present invention can be used to coat finished implants, prostheses, membranes, catheters, contact lenses, intraocular lenses, and other devices which are coated with a polymer according to the present invention to impart biocompatibility to the article.

The invention thus also provides a finished device comprising a surface having a coating thereon of a polymer of the present invention.

FIG. 1 compares scanning electron micrographs of a polyimide sheet treated and untreated with a copolymer of the invention and then contacted with blood. FIG. 1.(a) shows a scanning electron micrograph (1200 x) of an unsubbed, untreated poly(imide) sheet. FIG. 1.(b) shows a scanning electron micrograph (900 x) of a poly(acrylic acid) subbed poly(imide) sheet treated with poly (2(methacryloyloxyethyl)-2(trimethylammonium)ethyl phosphate-co-2-aminomethacrylate) (9:1), in accordance with Example 2.

DETDESC:
The present invention will now be further illustrated by the following Examples:

EXAMPLES

The following assays have been used to evaluate coatings of polymers according to the present invention.

Protein Adsorption Using an Enzyme Immunoassay

The assay determines adsorption of human fibrinogen at a surface. This protein is representative of protein which is typically adsorbed at a surface. The assay can be readily modified to determine the adsorption of other proteins.

Discs (7 mm in diameter) of untreated material (as controls) and material treated with polymer as described below, were prepared and washed with phosphate buffered saline (PBS) for at least 10 minutes in the wells of microplates. The samples were incubated with human plasma (300 mu l) for 10 minutes and then washed with PBS three times. Each of the test samples and each of the control samples were treated with human fibrinogen-specific

antibody (300 mu l) for 30 minutes and again washed with PBS three times. As a control for non-specific binding of antibody to the samples, each sample was also incubated with non-specific antibody (300 mu l) for 30 minutes. A conjugate of horseradish peroxidase and a second antibody specific to the first antibody (300 mu l) was added to both the test samples and the controls and incubated for 30 minutes before washing. Each of the test samples and the controls were transferred to new microplates and a solution of 2,2'-azino-bis(3-ethyl benzthiazoline-6-sulphonic acid) (ABTS) in phosphate-citrate buffer (300 mu l,0.6 mg/ml) added, the reaction was allowed to proceed for 10 minutes. At this time an aliquot of the mixture (200 mu) was removed and added to a solution of citric acid and sodium azide in distilled water (20 mu l, 0.21 g/ml and 2 mg/ml respectively). The optical density of the solutions was measured using a Techgen automated plate reader at 650 nm using the ABTS solution as blank.

In an alternative procedure, rather than using ABTS, each of-the samples was transferred to wells of new microplates and a solution of o-phenylene diamine (OPD) in phosphate-citrate buffer (300 mu l, 0.4 mg/ml) added, and the reaction was allowed to proceed for 10 minutes. At this time an aliquot of the mixture (200 mu l) was removed from each well and the optical density of the solutions was measured using a Techgen automated plate reader at 450 nm using the OPD solution as blank.

Activated Platelet Study

Blood was collected from a healthy adult volunteer using the double syringe method where the first 5 ml of blood is discarded. The blood was collected into tri-sodium citrate (32 g/l) in the proportion of 9 volumes to 1 volume citrate in plastic tubes. The samples were kept at room temperature on a spiral mixer until used.

Discs (7 mm in diameter) of untreated material as controls and material treated with polymers as described below were prepared and placed into the wells of a microplate. The samples were incubated with whole fresh citrated blood (200 mu l) on a rotary mixer for 30 minutes before washing in PBS four times. Platelet activation was measured by a proprietary assay [Lindon, J. N. et al., Blood, 68, 355 (1986)] and British Patent Application No. 91-25721.2].

In an alternative procedure half of the test replicates were incubated with citrated blood (200 mu l) and the remainder were incubated with EDTA-treated blood on a phase shaker for 30 minutes before washing in PBS four times. Platelet activation was measured in a manner similar to that described above for detection of proteins by enzyme immunoassay using antibodies against GMP140 to detect the presence of this platelet activation marker on the surface of biomaterials. In the presence of EDTA, which extracts calcium from inside platelets, activation is inhibited, so that incubation with EDTA-treated blood acts as a non-specific control for activation, obviating the need for incubation in non-specific antibody.

Heparin Activity

Loading of samples with heparin

Samples of filter strips were incubated with 5 ml of a solution of heparin in PBS (usually 50 U/ml). After 30 min, the samples were rinsed for 10 sec on both sides first with PBS then with deionized water. The samples were dried on tissue paper and in air and stored at room temperature.

Preparation of samples for heparin test

Heparin loaded filter strips (dip-coated or removed from whole arterial filters) were usually incubated for 5 hrs at 37o C. in PBS/BSA 1%/NaN3 0.1% to remove unstable bound heparin. The samples were then rinsed with PBS and deionized water as described and dried in air.

Samples of 0.2-0.4 x 0.4 cm were cut out and tested as described below.

Heparin test

A chromogenic assay (Heparin CRS106, Sigma). The "Semi-Micro Method" described in the manual was used. Heparin loaded coated samples were placed in polystyrene test tubes. The tubes were placed into a 37o C. water bath (5 tubes). 200 mu l of bovine factor Xa was added and the tubes were shaken. Following 1 min agitation, 200 mu l factor Xa substrate was added to the tubes and they were agitated for 5 min. 200 mu l acetic acid (> 90%) was added to the tubes and the tubes were shaken. 200 mu l of the solution was removed from the tubes and added to the well of a microplate (2 wells/sample) and measured at 405 nm against wells containing 200 mu l of PBS. Previous results had shown that PBS gave the same absorbance reading as a reagent blank. The heparin activity was calculated with the use of a standard curve prepared with soluble heparin.

Example 1

Preparation of poly(2(methyacryloyloxyethyl)-2(trimethylammonium)ethyl phosphate inner salt -co- 2-aminoethylmethacrylate) (9:1)

2(Methacryloyloxyethyl)-2(trimethylammonium)ethyl phosphate inner salt (9.96 g, 0.0335 mole) was dissolved in methanol (115 ml) . Water (10 ml) was added followed by the addition of 2-aminoethylmethacrylate (0.5571 g, 0.0034 mole). The solution was stirred (250 rpm) at 22o C. under a stream of nitrogen (70 ml/min) for 30 minutes. 2,2'Azo-bis(2-methylpropionitrile) 0.12 g, 0.73 mmole) was added and the flow of nitrogen was reduced to 9 ml/min, the temperature was raised to 60o C. The temperature and nitrogen flow rate were maintained for 16 hours.

The mixture was allowed to cool and transferred to centrifuge tubes. The samples were centrifuged for 30 minutes at 4000 rpm. The samples were combined and the polymer precipitated by dropwise addition to acetone (800 ml) . The acetone was decanted from the polymer and the polymer washed with acetone (200 ml) . The polymer was isolated by vacuum filtration under a nitrogen atmosphere and finally dried in vacuo overnight at room temperature. IR (cm< - 1> ;KBr disc) 3435, 2929, 2096, 1732, 1628, 1245, 1166, 1089, 970.

Example 2

Treatment of poly(acrylic acid) subbed poly(imide) sheets with poly(2(methacryloyloxyethyl)-2(trimethylammonium)ethyl phosphate inner salt-co-2-aminoethylmethacrylate) (9:1)

Poly(imide) samples were placed in the plasma chamber of a plasma barrel etcher and evacuated with a pump down to a pressure of 0.001 mbar. oxygen was then allowed to flow into the reactor. The plasma was started with 90 W forward power and nearly 0 W backward. The pressure was approximately 0.7 mbar. The plasma was turned on for 5 minutes, then the radio frequency generator (13.56 MHz) was switched off at the same time as the flow of oxygen stopped. The pressure was allowed to drop and the valve of the flask with acrylic acid was opened to let the monomer flow into the chamber (100% acrylic acid). The vacuum was decreased to 0.3 mbar. The high frequency generator was then started with 30 W forward power and OW backward power and the polymerisation carried out for 20 minutes. After switching off the high frequency generator and closing the valve to the acrylic acid, the chamber was evaporated again for another 5 minutes to remove all of the excess monomer.

The poly(acrylic acid) subbed poly(imide) was cut into 4 x 1.5 cm pieces and washed with distilled water. The squares were then added to a 1.25% solution (6.3 ml) of poly(2 (methacryloyloxyethyl)-2(trimethylammonium)ethyl phosphate inner salt-co-2-aminoethylmethacrylate (9:1). 1-Ethyl-3(3-dimethylaminopropyl)carbodiimide (20 g) was then dissolved in the solution and the pH then adjusted to 5.0 using hydrochloric acid (0.5M). After 1 hour the samples were removed, washed with distilled water and allowed to dry.

Visualisation of Platelet Activation on a Surface

Blood was collected from a healthy adult volunteer using the double syringe method where the first 5 ml of blood is discarded. The blood was collected into tri-sodium citrate (32 g/1) in the proportion of 9 volumes of blood to 1 volume citrate in plastic tubes. The samples were kept at room temperature on a spiral mixer until used.

1 cm<2 > samples of poly(2(methacryloyloxyethyl)-2-(trimethylammonium)ethyl phosphate inner salt-co-2-aminoethylmethacrylate) (9:1) coated poly(imide) as prepared above and of uncoated poly(imide) as a comparison were placed into 1 ml of the fresh citrated blood and incubated for 30 minutes on a spiral mixer at room temperature. The samples were then washed in phosphate buffered saline (PBS,pH7.4) prior to fixing in an aliquot of the following solution for 30 minutes.

2 ml 25% w/v glutaraldehyde

83 ml 0.15M PBS (pH7.4)

15 ml Saturated picric acid.

Picric acid increases the preservation of lipid-associated protein. The samples were again washed in PBS and then dehydrated using 70% and 100% methanol followed by 100% acetone prior to drying in air. Finally samples were sputter-coated with a platinum target (20 mAmps for 6 x 30 seconds) and observed at appropriate magnifications using a scanning electron microscope.

No platelet activation was seen on the coated poly(imide) samples whereas gross adhesion activation and aggregation were seen on the uncoated sample (see FIG. 1). The presence of the polymer on the surface was confirmed by the use of X-ray photoelectron spectroscopy (XPS). It can thus be seen that treatment of polyamide by first coating with a subbing layer of acrylic acid to render the surface reactive, and then coating with a copolymer according to the present invention substantially removed the haemostatic reaction to the polyamide.

Example 3

Preparation of poly(2 (methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt-co-3-chloro-2-hydroxypropyl methacrylate (1:1)

2 (methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt (7.46 g, 25.3 mmole), 3-chloro-2-hydroxypropyl methacrylate (4.51 g, 25.3 mmole) and p-toluene sulphonic acid monohydrate (0.1048 g, 0.55 mmnole) were dissolved in methanol (101 ml) . The solution was stirred (250 rpm) at 23o C. under a stream of nitrogen (50 ml/min) for 30 minutes. 2,2'-azo-bis(2-methylpropionitrile) (0.0843 g, 0.51 mmole) was added and the flow of nitrogen was reduced to 10 ml/min, the reaction temperature was raised to 60o C. This temperature and nitrogen flow rate were maintained for 16 hours.

The polymer was isolated from this mixture by precipitation in acetone (1500 ml), vacuum filtration and drying. The polymer was redissolved in methanol (40 ml) and isolated as before

using acetone (1000 ml).

The resulting polymer, obtained in 62% yield was a white solid.

NMR(200 MHz, d, ppm, CD3OD/CDCl3) 4.2-4.4 (b), 4.3-4.0 (b), 3.6-3.8 (b), 3.3 (s), 1.6-2.4 (b), 1.0-1.5(b), 0.7-1.0(b).

IR(cm< - 1> , KBr disc) 3416, 2959, 1727, 1655, 1490, 1247, 1165, 1088, 968, 792, 748.

Example 4

Preparation of poly(2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt-co-7dodecynmethacrylate (1:2)

The polymer was prepared by a method analogous to that described in Examples 4 and 6 using 2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt (8.41 g, 0.0285 mole) and n-dodecynmethacrylate (14.31 g, 0.0572 mole) dissolved 5 in propan-2-ol (160 ml) and ethyl acetate (60 ml).

The resulting polymer, obtained in 35% yield was a white powder.

NMR(100 MHz,d,ppm,CD3OD/CDCl3)4.2-4.4(b),3.8-4.2(b),3.6-3.8(b),3.3(s),2.25(s),1.8-2.2 (b),1.5-1.8(b),1.2-1.5(s), 0.8-1.0(s)

IR(cm< - 1> ,KBr disc) 3430, 2929, 2854, 1732, 1469, 1246, 1156, 108, 968, 788.

Elemental Analysis

Elemental Analysis

theory	C 65.1	H 9.0	N 1.8	P 3.9
actual	C 54.9	H 8.5	N 1.9	P 4.4

Relative Viscosity (chloroform/ethanol 50:50, 30o C.) 1.18.

The polymer may be crosslinked by gamma-irradiation or exposure to UV light which renders the polymer insoluble in dichloromethene/methanol.

A sample of stainless steel treated with the polymer showed a reduction in protein adsorption of 68% (determined by the enzyme immunoassay described above) and a reduction in platelet activation of 100% (determined by the platelet activation assay described above, using anti GMP 140) compared to untreated material. A sample of PVC coated with the polymer showed a reduction in protein adsorption of 60% compared to untreated material as determined by the same assay technique.

Example 5

Preparation of poly(2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt-co-n-dodecyl methacrylate-co-2 hydroxyethylmethacrylate) (17:75:8)

The polymer was prepared by a method analogous to Examples 4 and 6, using 2 (methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt (2.0 g, 0.0068 mole), n-dodecyl methacrylate (7.65 g, 0.0301 mole) and 2 hydroxyethyl methacrylate (0.42 g, 0.0032 mole) dissolved in propan-2-ol(70 ml) and ethyl acetate (30 ml).

The resulting polymer, obtained in 53% yield was a white solid.

NMR(100 MHz,d,ppm,CD3OD/CDCl3)4.2-4.4(b),3.8-4.2(b),3.6-3.8(b),3.3(s),1.8-2.2(b),1.5-1.8(b),1.2-1.5(s),0.8-1.0(s)

IR(cm< - 1> ,KBr disc) 3435, 2925, 2860, 1729, 1468, 1243, 1152, 1089, 969, 791.

A coating solution of poly(2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt-co-n-dodecyl methacrylate-co-2-hydroxyethylmetacrylate) (0.5097 g) in propan-2-ol (50 ml) was prepared. Aluminium sheet was washed with propan-2-ol, hexane and water and dried, the coating solution (0.5 ml) was applied to pieces of the aluminium sheet (7.5 cm) by a spin coating technique using a spin speed of 1200 rpm.

Example 6

Preparation of poly(2 (methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt-co-methacrylic acid (7:3)

The polymer was prepared by a method analogous to that of Examples 4 and 6 using 2 (methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt (4.44 g, 0.0149 mole), and methacrylic acid (0.54 g, 0.0063 mole) dissolved in propan-2-ol (25 ml) and water (25 ml). The polymer was isolated by precipitation in acetone (500 ml), redissolved in methanol (50 ml) and isolated by precipitation in diethylether (500 ml).

The resulting polymer, obtained in 30% yield was a white solid.

NMR(100 MHz,d,ppm,CD3OD/CDCl3)4.2-4.4(b),3.8-4.2(b),3.6-3.8(b),3.3(s),1.8-2.2(b),1.5-1.8(b),1.2-1.5(s),0.8-1.0(s)

IR(cm< - 1> ,KBr disc) 3430, 2929, 2854, 1732, 1469, 1246, 1156, 1089, 968, 788.

This-polymer was used to treat cellulose film which had been treated with 2-aminoethyl methacrylate as follows:

A section of cellulose dialysis membrane (4 x 6 cm) was taken, and placed into a solution of 2-aminopropylmethacrylate (3.34 g) and ceric ammonium nitrate (0.05 g) in distilled water (20 ml). The solution was deoxygenated with N3 for 10 minutes, then the vessel was sealed, and left at room temperature for 2 hours. The cellulose sample was then removed from the solution, then washed extensively in distilled water for 24 hours.

The presence of amine hydrochloride moieties on the grafted sample was demonstrated by the differential uptake of anionic and cationic dyes (Trypton blue and methylene blue respectively).

Strips of the functionalised cellulose (0.5 cm x 2 cm) were placed in a 10% w/w solution of the polymer in water. The samples were left to stand at room temperature for 1 hour, then washed extensively in distilled water (200 ml) for 2 hours.

Following the aqueous wash, the treated cellulose was placed into a solution of acid molybdate spray reagent and left to stand for 1 hour, then removed and washed with distilled

water. The presence of phosphate groups on the sample was demonstrated by the development of a blue colour.

Example 7

Preparation of poly(2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt-co-n-dodecylmethacrylate-co-3-trimethoxysilylpropylmethacrylate) and subsequent cross-linking of cast films

This example illustrates the preparation of a polymer containing 3-trimethoxysilylpropylmethacrylate for subsequent cross-linking, in addition to phosphorylcholine for biocompatibility.

2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt (9.6 g) was dissolved in 170 ml iso-propyl alcohol and stirred over molecular sieve (4A) for 0.5 hour. The solution was then filtered into the reaction flask and 16.6 g dodecylmethacrylate and 4.6 g 3-trimethoxysilylpropylmethacrylate added along with 70 ml ethylacetate and 0.0618 g AIBN (2,2'-azo-bis(2-methylpropionitrile)). Nitrogen was bubbled through the solution for 0.5 hour and the temperature raised to 60o C. The reaction was maintained at this temperature stirring under a nitrogen atmosphere for 23 hours, after which the solution was allowed to cool and approximately half the solvent removed under reduced pressure. The polymer was isolated by precipitation into acetone and collected by filtration, drying under vacuum. Yield 17 g of a white solid. Coatings of the polymer were prepared by casting a solution of the polymer (approximately 10% w/w in methanol) containing 0.15 w/w on dry polymer of dibutyltindilaurate on glass plates and drying at 50o C. for 12 hours.

Example 8

Preparation of poly(2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt-co-n-dodecylmethacrylate-co-3-chloro-2hydroxypropyl methacrylate) and biological testing of PE-coated films

This example illustrates the preparation of a polymer containing 3-chloro-2 hydroxypropyl methacrylate as a cross-linking monomer in addition to phosphorylcholine for biocompatibility.

2(methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt (69.41 g), n-dodecylmethacrylate (120.85 g), AIBN (0.3939 g) and 3-chloro-2 hydroxypropyl methacrylate (6.3 g) were dissolved in a mixture of iso-propylalcohol (1380 ml)/ethyl acetate (570 ml) and the solution degassed for 0.3 hour. The reaction mixture was then stirred at 60o C. under a nitrogen atmosphere for 40 hours, allowed to cool and then precipitated into a large excess of acetone. The polymer was collected by filtration and dried.

Films of the polymer on polyethylene sheets (previously cleaned in methylated spirits) were prepared by dip coating in a solution of the polymer in ethanol (10 mg ml< - 1>). Cross-linking of the films was achieved by incorporation of butylammonium hydroxide in the casting solution (30 mg/200 mg of dry polymer); cross-linking was demonstrated by the failure of the films to redissolve in solvent. A fibrinogen single antibody assay showed a significant reduction in fibrinogen binding for both the uncrosslinked film and cross-linked film compared to the uncoated PE substrate.

Example 9

a) Preparation of a Copolymer of HEMA-PC and allyl methacrylate 2:1

20.6 g of HEMA-PC, 4.4 g allyl methacrylate and 0.05 g AIBN were stirred in 250 cm of deoxygenated ethanol at 65o C. under a nitrogen atmosphere for 24 hours. After cooling, the solution was filtered and the solvent removed on a rotary evaporator. The resulting white powder was redissolved in dichloromethane/methanol (80/20) and precipitated in a large excess of acetone. The solid product was removed by decanting, filtered, reprecipitated again from dichloromethane/methanol and dried under reduced pressure at ambient temperature to yield approximately 20 g of a white solid which was readily soluble in ethanol and substantially free of gel. <1> H NMR delta (D2O); 5.9 (olefinic CH), 5.4 (olefinic CH2) 4.1, 3.8, 3.2 (NMe3), 1.9, 1.2 and 0.8. The 1H NMR spectrum was consistent with a 2:1 copolymer of HEMA-PC and allyl methacrylate with the allyl group being unreactive under the conditions of the polymerisation.

b) Coating of Polydimethylsiloxane (PDMS) with MPC/AMA Copolymer

25 2 x 1 cm squares of PDMS-sheet (20-40 Pharmelast, SF Medical) were treated in a plasma chamber under an air atmosphere at a power of 100 W for 1 minute on each side. They were then dip coated in a 5% w/v aqueous solution of MPC/AMA (previously filtered through a 0.2 um filter) for 5 minutes, rinsed briefly with deionised water and dried overnight at ambient temperature and humidity.

Dynamic contact angle analysis (DCA) of the samples was performed using a Cahn 1a with a borate buffered saline probe solution at a stage speed of 100 mu m/s. All results are quoted as average values for 5 samples. The advancing angle of the coated PDMS was 48 degrees and the receding angle was 39 degrees. For comparison, an uncoated PDMS sheet had an advancing angle of 105 and a receding angle of 59.

After cleaning with a surfactant-based contact lens cleaner (Miraflow, CIBA Vision) for 1 minute on each side, the advancing angle of the coated PDMS sheet was 53 degrees and the receding angle was 39 degrees. The minimal change in contact angle upon cleaning is evidence for a stable coating.

In previous experiments it had been shown that treatment of substrates coated with allyl methacrylate HEMA-PC copolymers resulted in additional stabilisation of the coating. Such a treatment may be advantageously applied to the products of this example.

Example 10

a) Synthesis of Terpolymer of HEMA-PC:dodecyl methacrylate 3-(trimethoxysilyl) propylmethacrylate 2:1:0.23)

HEMA-PC (9.74 g, 33 mmol) was dissolved in isopropyl alcohol (108 ml) and stirred under a blanket of nitrogen. After 20 minutes, dodecyl methacrylate (4.19 g, 16.5 mmol) and 3 (trimethoxysilyl)propylmethacrylate (1.05 g, 4.2 mmol) were added in ethyl acetate (42.5 ml). Nitrogen was bubbled through the mixture for 30 minutes, AIBN (0.025 g) was added and it was heated at 65o C. for 36 hours. After cooling to room temperature the polymer was isolated by precipitation into acetone (1500 ml). The material was filtered and dried under vacuum to give the product, 13.45 g, 90% yield.

<1> H-nmr - 300.13 MHz (CDCl3/CD3OD). delta = 0.8-1.0 (s), 1.0-1.2 (s), 1.25-1.5 (s), 1.75 (s), 3.2-3.4(s), 3.7-3.8 (s), 3.9-4.4 (m)

<13> C-nmr - 75.47 MHz (CDCl3/CD3OD). delta = 1 4 (s), 18 (broad), 19 (broad), 23, 25, 26, 27, 29, 30(d), 32, 45, 46, 54, 55, 60, 64 (d), 65, 66, 67, 68

<32 > P-nmr - 121.45 MHz (CDCl3CD3OD). delta = 0.4997 (s)

b) Treatment of Polypropylene with Polymer

An aqueous solution of sodium persulphate (10%, w/v) was taken and polypropylene pieces were added. The mixture was purged with nitrogen for 20 minutes before heating the mixture to 80o C. for two hours whilst maintaining the purging. Samples were removed and then coated by dipping in a solution of the polymer made in step a) (2 mg/ml) in ethanol. The materials were heated at 60o C. for 16 hours prior to testing.

Samples of treated polypropylene were incubated with plasma and the amount of fibrinogen determined using a single antibody ELISA assay. Coated samples were compared to untreated controls and the results are expressed in absorbance values (which are proportional to the total fibrinogen adsorbed on the surface) and as a relative percentage reduction comparing coated to uncoated samples:

Polymer treated polypropylene, mean absorbance (n = 5) = 0.068

Untreated polypropylene, mean absorbance (n = 5) = 1.214

Reduction in fibrinogen adsorption (Coated v uncoated) = 95%

Polypropylene strips were incubated with solutions of insulin and the amount of insulin adsorbed determined using a double antibody ELISA assay. Coated samples were compared to untreated controls and the results are expressed in absorbance values (which are proportional to the total insulin adsorbed on the surface) and as a relative percentage reduction comparing coated to uncoated samples:

Polymer treated polypropylene, mean absorbance (n = 3) = 0.105

Untreated polypropylene, mean absorbance (n = 3) = 0.962

Reduction in insulin adsorption (coated v uncoated) = 89%

c) Treatment of Glass with Polymer

Glass beads were pre-washed by sonication in ethanol (2 x 2 mins). After drying at ambient temperature, the beads were stirred for two minutes in hydrochloric acid (10M). The samples were then washed with distiled water until the washings were neutral after which they were dried in air. The beads were left in a solution of the polymer synthesised in step a) (5 mg/ml) in ethanol, removed and allowed to dry on a piece of polypropylene. The materials were heated at 60o C. for 16 hours prior to testing.

Glass beads were incubated with solutions of insulin and amount of insulin adsorbed determined using a double antibody ELISA assay. Coated samples were compared to untreated controls and the results are expressed in absorbance values (which are proportional to the total insulin adsorbed on the surface) and as a relative percentage reduction comparing coated to uncoated samples:

Polymer treated glass, mean absorbance (n = 7) = 0.110

Untreated glass, mean absorbance (n = 7) = 0.594

Reduction in insulin adsorption (coated v uncoated) = 82%

d) Treatment of Polymethylmethacrylate with Polymer

Polymethylmethacrylate pieces were coated by dipping in a solution of a polymer synthesised as in step a) but having a slightly higher level of reactive comonomer (0.26 mole per 1 mole of dodecyl methacrylate and 2 moles HEMA-PC) (10 mg/ml) in ethanol. The materials were heated at 60o C. for 16 hours prior to testing.

Samples of treated polymethylmethacrylate were incubated with plasma and the amount of fibrinogen determined using a single antibody ELISA assay. Coated samples were compared to untreated controls and the results are expressed in absorbance values (which are proportional to the total fibrinogen adsorbed on the surface) and as a relative percentage reduction comparing coated to uncoated samples:

Polymer treated polymethylmethacrylate, mean absorbance (n = 6) = 0.199

Untreated polymethylmethacrylate, mean absorbance (n = 5) = 2.788

Reduction in fibrinogen adsorption (Coated v uncoated) = 93%

Example 11

Quater polymers of HEMA-PC:dodecyl methacrylate:3-(trimethoxy-silyl)propylmethacrylate: 3-hydroxypropyl methacrylate (23:47:5:25)

A triple-necked round bottom flask (250 ml) was equipped with a Davis condenser, a nitrogen inlet, the, polymerisation solvent which is ethanol and a thermometer. The condenser was topped with a calcium chloride guard tube, and a magnetic follower was added to the flask. The reaction system then purged using nitrogen gas.

The HEMA-PC monomer was weighed and then stirred in the reaction solvent until dissolved. The comonomers were weighed and then stirred into the reaction solvent until dissolved. The initiator used throughout the polymer development was AIBN at a level of 2 w/w %, and this was dissolved into the reaction solvent.

The solutions were then filtered under vacuum using a buchner funnel, into the reaction vessel. The solution was degassed using a constant flow of nitrogen for a period of twenty minutes, after which time the nitrogen flow rate was reduced and the temperature increased to 62 C. The polymerisation was carried out under an atmosphere of nitrogen, and maintained at 62 C. for When the polymerisation had finished the heat source was removed and the solution was allowed to cool to room temperature. The solvent was removed using rotary evaporation techniques until the point at which the polymer began to foam. This solution was then further diluted with dichloromethane and precipitated by dropwise addition into acetone with constant stirring. The precipitate was then collected using vacuum filtration under a blanket of nitrogen and dried at 25 C. in vacuo for 16 hours.

The polymer was then cooled using liquid nitrogen and ground to a fine powder using an analytical mill. The polymer was then further dried in vacuo at 25 C. for 16 hours. The yield of polymer obtained was recorded.

Ethanol was the reaction solvent.

The polymer product had the following properties:

Elemental Analysis:

*	C	H	N	P	Si
Theoretical	62.59	9.91	1.37	3.02	0.60
Actual	60.65	9.88	1.43	3.06	0.59

Dilute Viscosity Measurements:

* Batch No.	Intrinsic Viscosity	Relative Viscosity	Mv
batch 1	0.1455	1.145	172769
batch 2	0.1404	1.140	160919
batch 3	0.1433	1.143	167718

Mv is Viscosity Average Molecular Weight and is expressed in Daltons.

The polymer was coated using dip coating from ethanol at 5 and 10 mg/ml. The coating speed was 3 mm/min. The polymer was cross-linked by heating at 70 C. for 4 hours or longer eg overnight.

The polymer was then used to coat a number of steel coronary devices crosslinked by heating and submitted to a number of tests which looked at the performance of the hydrogel coating during in vitro testing.

All of the SEM microscopy was carried out using a Hitachi S4000 field emission SEM. The samples were prepared by mounting on the stubs using conductive graphite pads. Sputter coating was not used.

Molecular weight, radius of gyration and second virial coefficients for the polymers were calculated from Zimm plots obtained through the use of static light scattering. The measurements were made using a PL-LSP light scattering photometer starting at 30 and increasing in 15o increments. The polymers were measured in ethanol with toluene used as the reference. A refractometer was used to establish the dn/dc value for the solutions.

Molecular weights for the polymer was found to be in the region of 200,000 daltons, with a radius of gyration of 14 nm.

The biological performance (fibrinogen adsorption) of the crosslinkable polymers has been shown to be good. The adsorption value was about 0.2 (comparative unit relating to absorbance in an ELISA test) for the PC polymer and about 1.8 for the uncoated steel.

An important property required of the final polymer coating is its mechanical stability. The angioplasty devices undergo several deformations and stresses when deployed, as such any coating must respond to these conditions. This is demonstrated in experiments, where coronary **stents** were coated with the quater polymer and a more brittle coating not containing the hydroxypropyl methacrylate monomer. The more brittle polymer coating ruptures under the stresses associated with balloon expansion. This is not the case when **stents** coated with the new polymer are subjected to the procedure.

Example 12

Preparation of poly(2-(Methacryloyloxyethyl)-2'-(Trimethylammoniumethyl)Phosphate, Inner Salt)-co-(n-Dodecyl methacrylate)-co-(2-(Methacryloyloxy)ethyl trimethylammonium

chloride)-co-(3-Trimethyoxysilylpropyl methacrylate) 30:60:6:4 quaterpolymers

12.1 Monomer Feed Synthesis

The zwitterionic monomer (40.68 g, 0.138 mole) and cationic monomer (5.73 g, 0.0275 mole) were weighed in a glove box environment dried by P2O5 Dodecyl methacrylate (69.45 g, 0.273 mole), trimethoxysilyl monomer (4.53 g, 0.0182 mole) and alpha -azo-isobutyronitrile (AIBN) initiator (1.202 g, 1%) were weighed in air. A 3 neck reaction flask, fitted with water condenser, nitrogen gas flow and monomer feed tubing, and primed with anhydrous n-propanol (60 g) solvent, was immersed in a heated 90o C. oil bath. The monomers and initiator were dissolved in 300 g of n-propanol solvent and magnetically stirred in a measuring cylinder sealed with parafilm. The reaction mixture was drawn into polypropylene tubing placed inside the measuring cylinder and through silicone tubing via a peristaltic pump to enter the heated reaction vessel in a dropwise process. A complete transfer to the heated vessel took 2.25 hours. The reaction was stirred for another hour. A second charge of AIBN initiator (0.12 g), dissolved in 3 ml n-propanol, was added and the reaction mixture was stirred for a further 50 min, taking the total reaction time to 4 hours.

Once cooled to room temperature, the reaction mixture was filtered through a sintered glass filter. The solvent was removed at 40o C.-50o C. by rotary evaporator to give a white foam residue that was later redissolved in 480 ml dichloromethane and 40 ml methanol solvent mixture and dropwise precipitated into 4000 ml acetone. A white solid product settled from the acetone leaving a slightly cloudy supernatant. The product was separated by Buchner flask and 113 Whatman wet strenghtened filter paper, and dried in a room temperature vacuum oven for up to 24 hours prior to a second workup and precipitation in acetone. The product was weighed (82.9 g) to provide a 68.9 wt % yield, bottled in a brown glass vial and refrigerated.

Characterisation of Product

The polymer requires by weight C 63.08%, H 10.13%, P 3.55%, N 1.93%, Si 0.43% Cl 0.81%, found C 58.1%, H 9.98%, P 3.09%, N 1.90%, Si 0.20%, <1> Hnmr (400 MHz, ppm, CD3OD:CDCl3 1:1 v:v) 4.34, 4.30, 3.98, 3.72, 3.38, 3.29, 3.22, 1.67, 1.32, 0.92, 0.10. Specific viscosity of 10 mg/ml solution in ethanol:chloroform (1:1 v:v) is 0.13. The polymer product was subjected to the chloride ion assay to establish the rate of inclusion of cationic monomer; required 4.76 wt %, found 4.82 wt % and 4.94 wt %.

12.2 One Pot Synthesis

Zwitterionic monomer (4.87 g, 1.65 x 10< - 2 > mole), dodecyl methacrylate (8.11 g, 3.19 x 10< - 2 > mole), cationic monomer (0.67 g, 0.32 x 10< - 2 > mole) and trimethoxy-silyl monomer (0.53 g, 0.21 x 10< - 2 > mole) were rinsed into the reaction vessel with 114 ml solvent mixture of 15:85 v/v % MeOH:EtOH. Anhydrous cationic monomer was predissolved in 3 ml pure MeOH before being rinsed into the reaction vessel. Dodecyl methacrylate monomer was pre-columned through activated basic alumina (Brockmann 1 ca.150 mesh, 50 g) before use. Dry nitrogen gas was bubbled through for 20 minutes to degas the reaction mixture at room temperature before immersing the reaction vessel in an oil bath heated to 67o C. The vessel was heated for 15 minutes prior to AIBN initiator (0.14 g) being rinsed into the reaction mixture with 2 ml solvent mixture. The reaction was magnetically stirred and maintained up a positive pressure nitrogen blanket sufficient to bubble through a mineral oil bubbler. The reaction time was 39 hours.

Once cooled to room temperature, the reaction mixture appeared clear with a slight haze. The solvent was removed at room temperature by rotary evaporator to give a white foam residue that was later redissolved in 50 ml dichloromethane and added dropwise into vigorously stirred 500 ml acetone. A white solid product settled from the acetone leaving a slightly cloudy supernatant. The product was separated by Buchner flask and 113 Whatman

wet strengthened filter paper, and dried in a room temperature vacuum oven for up to 72 hours. The product was weighed to provide a 91 wt % yield, bottled in a glass jar and refrigerated.

Characterisation

The polymer requires by weight C 62.93%, H 10.11%, P 3.61%, N 1.95%, Si 0.42% Cl 0.80%, found C 57.88%, H 10.20%, P 3.30%, N 1.84%, Si 0.12% Cl 0.78%; <1> Hnmr (400 MHz, ppm, CD3OD:CDCl3 1:1 v:v) 4.33, 4.29, 3.97, 3.71, 3.38, 3.34, 3.29, 3.22, 1.67, 1.32, 0.92, 0.09; specific viscosity in a 10 mg/ml solution of ethanol:chloroform (1:1) is 0.32.

Example 13

Preparation of poly(2-Methacryloyloxyethyl)-2'-(Trimethylammoniumethyl)Phosphate, Inner Salt)-co-n-Dodecyl methacrylate)-co-(2-Methacryloyoxy)ethyl trimethylammonium chloride)-co-(hydroxypropyl methacrylate)-co-(3-Trimethoxysilylpropyl methacrylate) 23:47:6:20:4 polymers

13.1 Monomer Feed Synthesis

Zwitterionic monomer (34.10 g, 0.116 mole) and cationic monomer (6.3 g, 0.030 mole) were weighed in a glove box environment dried by P2O5. Dodecyl methacrylate (60.01 g, 0.236 mole), hydroxypropyl methacrylate monomer (14.51 g, 0.101 mole), trimethoxysilyl monomer (5.00 g, 0.020 mole) and AIBN initiator (0.2409 g, 0.2%) were weighed in air. A 3 neck reaction flask, fitted with water condenser, nitrogen gas flow and monomer feed tubing, and primed with anhydrous n-propanol:isopropyl acetate (60:40 mass ratio) solvent, was immersed in a heated 90o C. oil bath. The monomers and initiator were dissolved in n-propanol:isopropyl acetate solvent and magnetically stirred in a measuring cylinder sealed with parafilm. The reaction mixture was drawn into polypropylene tubing placed inside the measuring cylinder and through silicone tubing via a peristaltic pump to enter the heated reaction vessel in a dropwise process. A complete transfer to the heated vessel took 2 hours. The reaction was stirred for another hour. A second charge of AIBN initiator (0.0241 g, 0.02 wt %) was added and the reaction mixture was stirred for a further hour, taking the total reaction time to 4 hours. Total solids content was 30 wt % in n-propanol:isopropyl acetate (168.06 g:112.08 g).

Once cooled to room temperature, the reaction mixture was split into two batches. The first batch of reaction mixture (240 ml) was precipitated by dropwise addition to vigorously stirred methyl acetate (2000 ml). The product was separated by Buchner flask and 113 Whatman wet strengthened filter paper, and dried in a room temperature vacuum oven for up to 24 hours. The product was rapidly frozen by liquid nitrogen, milled into a fine powder and further dried in a room temperature vacuum for 24 hours. The product (50.67 g, 81.8% based on mass recovery) was bottled in a brown glass vial and stored at 4o C.

The polymer requires by weight C 62.4%, H 9.9%, P 3.0%, N 1.9%, Si 0.4% Cl 0.8%, found C 57.0%, H 9.4%, N 1.7%, P 2.7%; <1> Hnmr (400 MHz, ppm, CD3OD:CDCl3 1:1 v:v) 4.41, 4.08, 3.83, 3.46, 3.40, 3.34, 2.07, 1.67, 1.43, 1.18, 1.04.

The product was subjected to chloride ion assay to establish the rate Of inclusion of cationic monomer: required 5.23 wt %, found 4.66 and 4.71 wt %.

13.2 One Pot Synthesis

Zwitterionic monomer (3.98 g, 1.35 x < - 2 > mole), dodecyl methacrylate monomer (7.009

g, 2.76 x < - 2 > mole), cationic monomer (0.733 g, 0.35 x 10< - 2 > mole), hydroxypropyl methacrylate (1.691 g, 0.67 x 10< - 2 > mole) and trimethoxysilyl monomer (0.585 g, 0.24 x 10< - 2 > mole) were rinsed into the reaction vessel with 98 ml solvent mixture of 15:85 v:v % MeOH:EtOH. Anhydrous cationic monomer was predissolved in 3 ml pure MeOH before being rinsed into the reaction vessel. Dodecyl methacrylate was pre-columned through activated basic alumina (Brockmann 1 ca.150 mesh, 50 g) before use. Dry nitrogen gas was bubbled through for 20 minutes to degas the reaction mixture at room temperature before immersing the reaction vessel in an oil bath heated to 67o C. The vessel was heated for 15 minutes prior to AIBN initiator (0.14 g, 1.1 wt %) being rinsed into the reaction mixture with 2 ml solvent mixture. The reaction was magnetically stirred and maintained under a positive pressure nitrogen blanket sufficient to bubble through a mineral oil bubbler. The reaction time was 39.5 hours.

Once cooled to room temperature, the reaction mixture was filtered through sintered glass. The solvent was removed at < 40o C. by rotary evaporator to give a white foam residue that was later redissolved in 58 ml dichloromethane and added dropwise into vigorously stirred 600 ml acetone. A white solid product settled from the acetone leaving a slightly cloudy supernatant. The product was separated by Buchner flask and 113 Whatman wet strengthened filter paper, and dried in a room temperature vacuum oven for up to 20 hours. The product was milled, further dried in a room temperature vacuum for 24 hours and weighed to provide a 93.2 wt % yield, bottled in a glass jar and refrigerated.

The polymer requires by weight C 62.41%, H9.91%, P 2.99%, N 1.70%, Si 0.47%, Cl 0.89%, found C 58.45%, H 9.45%, P 2.55%, N 1.65% Si 0.34%, Cl 1.06%.<1> Hnmr (400 MHz, ppm, CD3OD:CDl3 1:1 v:v) 4.33, 4.29, 3.97, 3.71, 3.38, 3.34, 3.29, 3.22, 1.67, 1.32, 0.92, 0.09. Specific viscosity of 10 mg/ml solution in ethanol is 0.33. The polymer product was subjected to the chloride ion assay to establish the rate of inclusion of cationic monomer; required 5.24 wt %, found 5.16 wt % and 5.26 wt %.

13.3 Performance

The polymer was used to coat arterial filter devices. The filter was air plasma treated for 30s prior to coating. In a separate step two dispersions were made up. The first contained 2500U heparin (bovine lung) in PBS (2.5 ml) and water (47.5 ml) . The second contained 250 mg polymer in 50 ml isopropylalcohol. The two liquid compositions were mixed together then poured into the plasma treated filter which was shaken vigorously for 15 minutes to ensure contact of all the surfaces of the device with the coating mixture. The mixture was then drained out and the coated device washed three times with water. The rinsed filter was dried and placed in an oven overnight at 50o C. to ensure the reactive groups of the polymer had crosslinked.

Example 14

Performance of Polymers of Examples 12 and 13

Samples of polymers of examples 12 and 13 were coated onto arterial filters from 10 mg/ml solutions in isopropanol. The filters were dip coated with the polymer solutions, which were then dried overnight. The coated polymers were kept at 70o C. overnight to ensure complete crosslinking. The filters were then tested for their fibrinogen adsorption using the performance test described above. Some samples of filter were, after coating with polymer, loaded with heparin using the general test described above and then subjected to fibrinogen adsorption and heparin activity tests. The control was untreated filter. Table 1 shows the results for reduction in fibrinogen adsorption as compared to the control and heparin activity for the heparin loaded devices. Comparisons are quoted for two commercially available heparin coatings Medtronic CB-M40, believed to have covalently (end point attached) heparin and Medtronic M-40 believed to have tonically bound heparin, in terms of fibrinogen

adsorption and heparin activity. The results show that heparin is adsorbed onto the polymer, the mechanism assumed to be an ion exchange process. The filters coated with the PC polymer have reduced fouling by fibrinogen.

TABLE 1

Polymer of Example	Without Heparin Loading % reduction fibrinogen	With Heparin Loading * % reduction fibrinogen	Heparin activity MU/cm<2>
Control	0	100	
12	90	82	14
13	91	88	13
comparison covalently bound Heparin	N/A	56	9
comparison ionically bound Heparin	N/A	7	< 1

Reference Example 1

Preparation of 2(methacryloyloxyethyl)-2'(trimethylammonium ethyl phosphate inner salt

The preparation is illustrated by the reaction scheme A which follows.

a) 2-Chloro-1,3-dioxaphospholane (1)

In a flask fitted with a pressure equalising dropping funnel, reflux condenser (fitted with a CaCl2 guard tube) and magnetic stirrer, was placed a solution of phosphorus trichloride (220 ml; 346.3 g; 2.52 mol) in dichloromethane (500 ml). Ethylene glycol (139 ml; 154.7 g, 2.49 mol) was then added dropwise via the dropping funnel at such a rate that the evolution of HCl did not become too excessive. On the addition of the ethylene glycol, the condenser was arranged for distillation, and the dichloromethane removed at atmospheric pressure. When the distillate temperature reached 60o C. the flask was arranged for 5 vacuum distillation using a water pump, Distillation then gave 2-chloro-1,3-dioxaphospholane (158 ml; 224.5 g; 71.3) as a colourless mobile liquid (which fumes in moist air) b.pt. 36-40o C./21 mm Hg. [cf 45.5-47o C./20 mm Hg, Lucas et al, J. Am. Chem. Soc., 72, 5491, (1950)].

IR (cm< - 1> , thin film) 2980, 2905, 1470, 1210, 1005, 930, 813, 770.

b) 2-Chloro-2-oxo-1,3,2-dioxaphospholane (2)

In a flask fitted with a magnetic stirrer, reflux condenser (fitted with a CaCl guard tube) and sintered glass gas inlet tube, was placed a solution of 2-chloro-1,3,2-dioxaphospholane (100.8 g; 0.797 mol) in dry benzene (200 ml). The solution was stirred and a steady stream of oxygen was bubbled through the solution. The reaction was mildly exothermic, and temperature control was achieved by allowing the solvent to reflux. The oxygen was passed through the reaction mixture for 6 hours. The solvent was removed by rotary evaporation, and the colourless mobile residue distilled to give 2-chloro-2-oxo-1,3,2-dioxaphospholane (2) (87.41 g; 77%) as a colourless mobile liquid -b.pt 95-97o C./0.2 mbar [c.f. 102.5-105o C./1 mbar (Edmundson, Chem. Ind. (London)), 1828 (1962); 79o C./0.4 mbar (Umeda et al., Makromol. Chem. Rapid Commun., 3, 457, (1982)].

IR(cm< - 1> , thin film) 2990, 2910, 1475, 1370, 1310, 1220, 1030, 930, 865, 830.

c) 2(2-Oxo-1,3,2-dioxaphospholan-2-yloxy)ethyl methacrylate (3)

In a flask fitted with a magnetic stirrer, low temperature thermometer, and a pressure equalising funnel fitted with a silica gel guard tube; was placed a solution of 2-hydroxyethylmethacrylate (20.00 g, 0.154 mol) and triethylamine (15.60 g; 0.154 mol) in dry diethyl ether (300 ml). The solution was stirred and cooled to between - 20o C. and - 30o C. A solution of freshly distilled 2-chloro-2-oxo-1,3,2-dioxaphospholane(2) (21.9 g; 0.154 mol) in dry diethyl ether (20 ml) was then added dropwise over 30 minutes, the temperature being held at - 20o C. during the addition. Stirring was continued at this temperature for a further 1 hour and then for a further hour as the reaction mixture was allowed to warm to room temperature. The precipitated triethylamine hydrochloride was removed by filtration, and was washed well with dry ether. The ether was removed from the combined filtrate and washings by rotary evaporation. The cloudy oil residue was then shaken for 5 minutes with dry diethyl ether (50 ml) to precipitate a further crop of triethylamine hydrochloride, which was again removed by filtration. Removal of the ether on the rotary evaporator gave (3) (34.18 g; 94.3%) as a colourless viscous oil. IR (cm< - 1> , thin film) 1720, 1640, 1450, 1360, 1310, 1290, 1170, 1030, 930, 850.

NMR (CDCl3; 60 MHz, delta ppm) 1.95 (s,3H), 4.25-4.70 (m,8H), 5.70 (m,1H), 6.25 (m,1H). Rf 0.9 (SiO3, eluting with 10% methanol:90% dichloromethane; spot visualised with molybdenum blue spray reagent and with iodine vapour).

d) 2(Methacryloyloxyethyl)-2'(trimethylammonium)ethyl phosphate inner salt (4)

The phospholane (3) (67.20 g; 0.285 mol) was dissolved in 100 ml of dry acetonitrile, and placed in a heavy walled tissue culture bottle. The phospholane solution was then treated with a solution of anhydrous trimethylamine (25.74 g; 0.436 mol) in dry acetonitrile (100 ml). The vessel was then sealed, and placed in a water bath held at 50o C. for 30 hours. The vessel was opened, and the solution brought to the boil. The solution was filtered whilst hot, and then set aside for crystallisation.

The product was collected by filtration, and most of the solvent removed by suction. The wet product was then washed thoroughly with anhydrous ether, then dried under reduced pressure, to give (4) as a white amorphous, hygroscopic solid (51.16 g; 61%). Evaporation of the mother liquor gave a very viscous oil (20.00 g; 23%), from which further product (4) crystallised on standing at - 200 C. TLC (silica gel plates, eluting with methanol/dichloromethane (1:1 v/v)) showed one spot Rf 0.1, which was revealed with Dragendorff's reagent, Molybdenum blue spray reagent, and iodine vapour. IR(cm< - 1 > 1720, 1640, 1320, 1300, 1230, 1170, 970, 750.

NMR (D2O; 60 MHz; delta ppm) 2.0 (s,3H), 3.27 (s,9H) 3.60-4.50 (m, 8H), 5.80, (m,1H) and 6.25 (m,1H). CHN Found: C 42.98%, H 7.88%, N 4.42%, P 10.51%. CHN Theory: C 44.75%, H 7.46%, N 4.75%, P 10.51%.

Reference Example 2

Dodec-7-yn-1-ol Methacrylate

To dodec-7-yn-l-ol (25 g) in dichloromethane (60 ml) was added distilled triethylamine (14.1 g). The mixture was cooled in an ice bath (0.5o C.) and stirred as distilled methacryloyl chloride (16.2 g) in dichloromethane (50 ml) was added over 10 minutes. The temperature of the reaction was allowed to warm to ambient and the mixture stirred for two hours. Water

(150 ml) was added and the organic layer was removed and successively extracted with water (2 x 150 ml) and saturated sodium bicarbonate solution (2 x 150 ml), washed with brine (150 ml) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to give a pale yellow oily liquid which was distilled under reduced pressure (0.18 mBar, 106-110o C.) in the presence of copper (1) chloride to give dodec-7-yn-1-ol methacrylate, 17 g, 50% yield.

<1> H-NMR (200 MHz,d,ppm,CDCl3): 0.90 (t,3H), 1.45 (m,10H) 1.70 (m,2H), 1.95 (s,3H), 2.15 (m,6H), 4.15 (t,2H), 5.55 (s,1H), 6.10 (s,1H). [See Original Patent for Chemical Structure Diagram]

Steps (a) to (d) correspond with the steps in Reference Example 1. [See Original Patent for Chemical Structure Diagram]

CLAIMS: What is claimed is:

[*1] 1. A substantially non-cross-linked polymer formed by radical polymerisation of radical polymerisable monomers including

i) a zwitterionic monomer having the formula:

Y-B-X(I)

wherein

B is a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene chain optionally containing one or more fluorine atoms up to and including perfluorinated chains, or if X contains a carbon-carbon chain between B and the centre of permanent position charge or if Y contains a terminal carbon atom bonded to B, a valence bond;

X is a zwitterionic group selected from groups IVC, IVD and IVF in which

group IVC has the formula [See Original Patent for Chemical Structure Diagram]

the groups R<7 > are the same or different and each is hydrogen or C[1-4]alkyl, and e is from 1 to 4;

group IVD has the formula [See Original Patent for Chemical Structure Diagram]

the groups R<8 > are the same or different and each is hydrogen or C[1-4]alkyl, R<8a > is hydrogen or a group -C(O)B<1> R<8b > wherein R<8b > is hydrogen or methyl, B<1 > is a valence bond or straight or branched alkylene, oxaalkylene or oligo-oxaalkyene group, and f is from 1 to 4; and if B is other than a valence bond z is 1 and if B is a valence bond z is 0, if X is directly bonded to an oxygen or nitrogen atom and otherwise z is 1;

group IVE has the formula [See Original Patent for Chemical Structure Diagram]

the groups R<9 > are the same or different and each is hydrogen or C1-C4 alkyl, R<9a > is hydrogen or a group -C(O)B<2> R<9b> , wherein R<9b > is hydrogen or methyl, B<2 > is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group, and g is from 1 to 4; and

if B is other than a valence bond z is 1 and if B is a valence bond z is 0 if X is directly bonded to an oxygen or nitrogen atom and otherwise z is 1; and

group IVF has the formula [See Original Patent for Chemical Structure Diagram]

the groups R<10 > are the same or different and each is hydrogen or C[1-4]alkyl, R<10a > is hydrogen or a group -C(O)B<3> R<10b > wherein R<10b > is hydrogen or methyl, B<3 > is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group, and h is from 1 to 4; and

if B is other than a valence bond z is 1 and if B is a valence bond z is 0 if X is directly bonded to the oxygen or nitrogen and otherwise z is 1 and

Y is an ethylenically unsaturated polymerisable group selected from [See Original Patent for Chemical Structure Diagram]

R is hydrogen or a C1-C4 alkyl group;

A is -O- or -NR<1> - where R<1 > is hydrogen or a C1-C4 alkyl group or R<1 > is -B-X where B and X are as defined above; and

K<2 > is a group -(CH2)[p]OC(O)-, -(CH2)[p]C(O)O-, -(CH2)[p]OC(O)O-, -(CH2)[p]NR<2> -, -(CH2)[p]NR<2> C(O)-, -CH2)[p]C(O)NR<2> -, -(CH2)[p]NR<2> C(O)-, -(CH2)[p]OC(O) NR<2> -, -(CH2)[p]NR<2> C(O)NR<2> -, (in which the groups R<2 > are the same or different) -(CH2)[p]O-, -(CH2)[p]SO3-, or, optionally in combination with B, a valence bond and p is from 1 to 12 and R<2 > is hydrogen or a C1-C4 alkyl group and

ii) a monomer having a reactive group of the formula general formula (XII)

Y<2> -B<7> -Q<3(XII)>

where

Y<2 > is an ethylenically unsaturated polymerisable group selected from [See Original Patent for Chemical Structure Diagram]

R<26 > is hydrogen or C1-C4 alkyl;

T is -O- or NR<27> -, wherein R<27 > is hydrogen or a C1-C4 alkyl group or R<27 > is a group -B<7> Q<3> ;

B<7 > is a valence bond a straight or branched alkylene oxaalkylene or oligo-oxaalkylene group;

K<2 > is a group -(CH2)[q]OC(O)-, -(CH)[q]C(O)O-, -(CH2)[q]OC(O)O-, -(CH2)[q]NR<20> -, -(CH2)[q]NR<20> C(O)-, -(CH2)[q]C(O)NR<20> -, -(CH2)[q]NR<20> C(O)O-, -(CH2)[q] OC(O)NR<20> -, -(CH2)[q]NR<20> C(O)NR<20> - (in which the groups R<20 > are the same or different), -(CH2)[q]O-, or -(CH2)[q]SO3-, or a valence bond and q is from 1 to 12 and R<20 > is hydrogen or a C1-C4 alkyl group; and

Q<3 > is a reactive group selected from the group consisting of aldehyde groups; silane and siloxane groups containing one or more substituents selected from halogen atoms and C[1-4]-alkoxy groups; hydroxyl; amino; carboxyl; epoxy; -CHOHCH2Hal (in which Hal is selected from chlorine, bromine and iodine atoms); succinimido; tosylate; triflate; imidazole carbonyl amino; optionally substituted triazine groups; cinnamyl; ethylenically and acetylenically unsaturated groups; acetoacetoxy; methylol; and chloroalkylsulphone groups.

[*2] 2. A polymer according claim 1 in which Q<3 > is selected from the group consisting of aldehyde, reactive silane and siloxane, amino, epoxy, CHOHCH2Hal (in which Hal is halogen), succiinimido, tosylate, triflate, imidazolecarbonyl amino and optionally substituted triazine groups.

[*3] 3. A polymer according to claim 1 in which the group Q<3 > is selected from the group consisting of amino, acetylenically unsaturated hydrocarbon groups, 3-chloro-2-hydroxy-propyl and 3-trimethoxy silyl propyl.

[*4] 4. A polymer according to claim 1 in which the said monomer being a reactive group is selected from the group consisting of 2-aminoethylmethacrylate, 7-dodecynmethacrylate, 3-chloro-2-hydroxypropylmethacrylate and 3-(trimethoxysilyl)propylmethacrylate.

[*5] 5. A polymer according to claim 1 in which said radical polymerisable monomers include a comonomer having the general formula (VI)

Y<1> -Q(VI)

where

Y<1 > is an ethylenically unsaturated polymerisable group selected from [See Original Patent for Chemical Structure Diagram]

R<14 > is hydrogen or C1-C4 alkyl,

A' is -O- or -NR<15> - where R<15 > is hydrogen or a C1-C4 alkyl group or R<15 > is a group Q;

K<1 > is a group -(CH2)1OC(O)-, -(CH2)1C(O)O-, -(CH2)1OC(O)O-, -(CH2)1NR<16> -, -(CH2)1NR<16> C(O)-, -(CH2)1C(O)NR<16> -, -(CH2)1NR<16> C(O)O-, -(CH2)1OC(O) NR<16> -, -(CH2)1NR<16> C(O)NR<16> - (in which the groups R<16 > are the same or different), -(CH2)1O-, -(CH2)1SO3-, a valence bond and 1 is from 1 to 12 and R<16 > is hydrogen or a C1-C4 alkyl group; and

Q is selected from the group consisting of straight and branched alkyl, alkoxyalkyl and (oligo-alkoxy)alkyl groups containing 6 to 24 carbon atoms, any of which groups is unsubstituted or substituted by one or more fluorine atoms and optionally contains one or more carbon-carbon double or triple bonds; and

siloxane groups (CR<16a> 2)[qq](SiR<16b> 2)(OSiR<16b> 2)[pp]R<16b > in which each group R<16a > is the same or different and is selected from the group consisting of hydrogen, alkyl groups of 1 to 4 carbon atoms and aralkyl groups, each group R<16b > is alkyl of 1 to 4 carbon atoms, qq is from 1 to 6 and pp is from 0 to 49.

[*6] 6. A polymer according to claim 5 in which [See Original Patent for Chemical Structure Diagram]

R<14 > is methyl;

A' is -O- and

Q is an alkyl group of the formula -(CR<17> 2)[m]CR<17> 3, wherein the groups -(CR<17> 2)- are the same or different and in each group -(CR<17> 2)- the groups R<17 > are the same or different and each group R<17 > is selected from the group consisting of hydrogen, C[1-4]-alkyl and -fluoroalkyl and fluorine and m is in the range 5 to 23.

[*7] 7. A polymer according to claim 6 in which the said comonomer is selected from the group consisting of n-dodecyl methacrylate, octadecyl methacrylate, hexadecyl methacrylate, 1H,1H,2H,2H-heptadecafluorodecyl methacrylate, p-octyl styrene, p-dodecyl styrene and monomethacryloyloxypropyl terminated siloxanes.

[*8] 8. A polymer according to claim 7 in which the said comonomer is dodecyl

methacrylate.

[*9] 9. A polymer according to claim 1 in which the said radical polymerisable monomers include a diluent monomer selected from the group consisting of C[1-4]-alkyl(alk)acrylates, N,N-dialkylamino alkyl(alk)acrylates containing 1 to 4 carbon atoms in each N-alkyl group and 1 to 4 carbon atoms in the alkylene group, C[1-4]-alkyl(alk)acrylamide, hydroxy C[1-4]-alkyl(alk)acrylate, N-vinyl lactam having 5-7 atoms in the lactam ring, styrene, derivatives of styrene having ring substituents selected from C[1-4]-alkyl groups and halogen atoms, polyhydroxyl (alk)acrylates, alkenes, butadiene, maleic anhydride and acrylonitrile.

[*10] 10. A polymer according to claim 9 in which the diluent monomer is selected from hydroxy C[1-4]-alkyl(alk)acrylates and polyhydroxyl(alk)acrylates.

[*11] 11. A polymer according to claim 1 in which the said radical polymerisable monomers include at least 5% by weight zwitterionic monomer and at least 0.1% by weight monomer having a reactive group.

[*12] 12. A polymer according to claim 1 in which the said radical polymerisable monomers include at least 5% by weight zwitterionic monomer and 0.1% to 20% by weight monomer having a reactive group.

[*13] 13. A polymer according to claim 9 in which the radical polymerisable monomers include at least 5% by weight zwitterionic monomer, at least 0.1% by weight monomer having a reactive group and 5 to 20% by weight diluent monomer.

[*14] 14. A polymer according to claim 5 in which the said radical polymerisable monomers include at least 5% by weight zwitterionic monomer, at least 0.1% by weight monomer having a reactive group and 5 to 90% by weight of said comonomer.

[*15] 15. A liquid coating composition containing a polymer according to claim 1 and a solvent for the polymer.